Meniscus Transplantation Study Group
2008 Meeting

Meeting Program

Wednesday, March 5th, 2008
1:00 PM – 3:30 PM

San Francisco Marriott, Salon 1
55 Fourth Street
San Francisco, California 94103

2008 Meniscus Transplantation Study Group

Wednesday, March 5th, 2008 1:00 – 3:30 PM
San Francisco Marriott, Salon 1
San Francisco Marriott, 55 Fourth Street
San Francisco, California 94103
At the 2008 AAOS Annual Meeting, San Francisco, CA

Meeting Agenda:

INTRODUCTION: ***1:00 – 1:10***

Kevin R. Stone, MD, Chairman
Update on Meniscus Allograft Transplantation in Arthritis

Peter C.M. Verdonk, MD, Moderator

PRESENTATIONS:

Collagen Meniscus Implants (CMI) decrease reoperation rates in chronic knee patients compared to meniscectomy only: A 5-year survivorship analysis ***1:11 – 1:23***
Presented by William G. Rodkey, DVM

The Spatial Relationship of Type II collagen to the Blood Vessels in Immature and Mature Canine Menisci ***1:24 – 1:36***
Presentation by Cahir McDevitt, PhD

Generation and characterization of a human acellular meniscus scaffold for tissue engineering ***1:37 – 1:49***
Presented by Thomas Tischer, MD

Imaging findings after meniscal repair with degradable polyurethane scaffold: preliminary results ***1:50 – 2:02***
Presented by Peter Verdonk, M.D, PhD

Dynamic contact mechanics of a scaffold for partial meniscal replacement ***2:03 – 2:15***
Presented by Russell F. Warren, MD

Tissue Engineering approach for repair of Meniscal Defects in the avascular zone. What is the best cell source? ***2:16 – 2:28***
Presented by Peter Angele, MD

The reproducibility of radiographic measurement of lateral and medial meniscus horn position ***2:29 – 2:41***
Presented by Philippe Wilmes, MD

Arthroscopic lateral Meniscal Allograft : Preliminary results at one year with clinical outcome and Arthro-MRI assessment ***2:42 – 2:56***
Presented by Philippe Hardy, MD

Industry Review Panel: ***2:57 – 3:15***

1. Sterilization of Meniscus Allografts
2. Market Demands of Meniscus Allografts
3. Pricing and Reimbursement of Meniscus Allografts

Collagen Meniscus Implants (CMI) decrease reoperation rates in chronic knee patients compared to meniscectomy only: A 5-year survivorship analysis

William G. Rodkey, DVM
Steadman Hawkins Research Foundation, Vail, Colorado USA

Objectives: Meniscus loss leads to decreased clinical function and activity levels and increases the rate of knee degeneration, thus leading to additional surgeries or even knee replacement, especially in chronic patients. Chronic patients are more focused on preserving their knees and avoiding additional surgeries. The objective of this study was to determine if replacement of lost or irreparable meniscus tissue with the Collagen Meniscus Implant (CMI) decreased the need for additional surgeries in multi-operated chronic knee patients compared to meniscectomy only. We hypothesized that patients who gained meniscus tissue with the CMI would require fewer surgeries than meniscectomy only controls.

Methods: In this prospective randomized multicenter clinical trial (Level of Evidence I), patients 18 to 60 years old who had undergone one to three prior partial medial meniscectomies and currently had clinical symptoms of meniscus pathology were randomized either to receive the CMI or have an additional partial meniscectomy (control). Eighty-five CMI were implanted, but one was removed at 3weeks after an incision wound infection. The remaining 84 CMI patients were compared to 66 controls over 5 years to determine survivorship. Survivorship was defined as not having an additional unplanned surgery outside the experimental protocol on the study knee.

Results: Follow-up rate at 5 years was 96%. Eight CMI patients (9.5%) and 15 control patients (22.7%) required reoperation through 5 years. Survivorship at one year was 90% for control and 95% for CMI patients, 86% for control and 95% for CMI patients at 2 years, 83% and 92% at 3 years, 79% for control patients and 91% for CMI patients at 4 years, and 74% for control patients and 89% for CMI patients at 5 years (Figure). CMI patients had a significantly higher survivorship compared to controls ($p=0.04$). The risk (odds) of reoperation was 2.7 times greater for controls compared to CMI patients at 5 years (95% CI=1.2 to 6.7). Furthermore, the majority of control patient reoperations occurred prior to 24 months, but only four CMI reoperations occurred during the first 24 months.

Conclusion: This study confirms that chronic patients who received the CMI required fewer additional surgeries in their multiply operated knees than meniscectomy only controls through 5 years. The additional tissue regeneration supported by the CMI may decrease progression of degenerative changes and reduce the necessity and frequency for additional surgeries. This study further confirms the importance of preserving as much meniscus tissue as possible at the time of meniscus surgery, and clearly it supports the potential positive benefits of regrowing or regenerating lost meniscus tissue. Our hypothesis was affirmed.

The Spatial Relationship of the Vasculature to Type II Collagen and Tenascin-C in the Mature and Immature Canine Meniscus:

McDevitt, C. A., Chakrabarti, A. and Ochoa-Chaar, C. I. N.
Department of Biomedical Engineering, Lerner Research Institute and The Orthopaedic Research Center, The Cleveland Clinic, Cleveland, Ohio.

Blood vessels are present throughout most of the body of the meniscus in development. In skeletally mature animals, however, the meniscus is predominantly avascular with only 10-15% of the radial distance of the tissue occupied by vessels. Establishing which matrix molecules are specifically localized in the vascular and non-vascular zones of the knee joint meniscus is important in the choice of molecular markers for assessing the efficacy of repair or regenerative processes in this tissue.

Coronal sections from mature (> 14 months) and immature (10 weeks) canine menisci were stained with antibodies against von Willebrand factor, type I and type II collagen and tenascin-C.

In the immature meniscus, the blood vessels penetrated through most of the tissue. The complete tissue stained for type I collagen. No type II collagen was demonstrable in this tissue.

In the mature meniscus the von Willebrand factor staining for blood vessels was confined to the outer 12% of the radial distance. The type I collagen was distributed throughout the whole tissue. The tenascin-C staining was confined to the vascular and superficial zones. The type II collagen stained the middle and inner zones of the tissue and was abruptly absent where blood vessels were present. Thus, tenascin-C and type-II collagen selectively stain the extracellular matrices in the vascular and non-vascular zones of the meniscus respectively.

Supported by grants from the Department of Defense, DAMD 17-02-1-0677, and the National Football League Charities.

Generation and characterization of a human acellular meniscus scaffold for tissue engineering

Tischer T[1,3], Sandmann GH[1], Eichhorn S[2], Vogt S[1], Milz S[4], Imhoff AB[1]

[1]Department of Orthopaedic Sport Surgery, Technical University (TU) Munich, Germany
[2]Department of Orthopaedic Surgery, Biomechanics Section, TU Munich, Germany
[3]Department of Anatomy, Ludwig-Maximilians-University Munich, Germany
[4]AO Research Institute, AO Foundation, Davos, Switzerland

Introduction

Meniscus tears are one of the most frequent indications for arthroscopic operations of the knee joint. In cases of total meniscectomy, allografts or synthetic meniscus scaffolds like collagen meniscus implant (CMI) have been used with varying success to prevent early degenerative joint disease. Challenges regarding reduced initial and long-term stability prevent widespread clinical use so far. Recently the use of detergents like sodium dodecyl sulfate (SDS) has become popular to acellularize different tissues for use as scaffolds for further tissue engineering [1,2]. Therefore, the aim of this study was to develop a new construct for tissue engineering of human meniscus based on an acellular meniscus allograft to avoid the problems mentioned above.

Material and Methods

Medial and lateral menisci (n=16) of human cadavers from the department of forensic medicine were sampled and acellularized using the detergent sodium dodecyl sulfate (SDS) as the main ingredient or served as control group. In preliminary tests, the optimal processing time and SDS concentration for complete acellularization was evaluated. For final experiments ten menisci were used. These acellularized constructs were characterized biomechanically with a universal testing machine (Zwicki 1120; Zwick, Ulm, Germany) using a repetitive ball indention test (Stiffness N/mm, residual force N and relative compression force N were measured to investigate viscoelastic behavior) and compared to native menisci. Histological (hematoxylin–eosin, phase-contrast) as well as immunohistochemical (collagen 1,2 and 6) staining was performed with special emphasis on residual cell nuclei and structure of the extracellular matrix.

Results

Histologically, the processed menisci were completely cell-free. Biomechanical properties were identical to the native menisci samples in terms of stiffness ($p>0.05$, figure 1), residual force ($p>0.05$) and compression ($p>0.05$). No differences between medial and lateral menisci was observed. The collagen fibre arrangement as seen in phase contrast microscopy was not altered by the chemical processing. Immunohistochemical staining showed the unaltered distribution of the collagens I, II and VI, compared to native menisci.

Discussion

The acellularization using detergents like sodium dodecyl sulfate has the advantage of complete cell removal while preserving the extracellular matrix (no digesting enzymes are used) and thereby providing good biomechanical characteristics. The removal of the immunogenic cell components should prevent immunogenic reactions and lead to fast remodelling and incorporation of the scaffold into the host tissue. In future experiments these scaffolds should be seeded with autologous cell to further enhance remodelling and long-term stability.

References

1. Tischer T, Vogt S, Aryee S, Steinhauser E, Adamczyk C, Milz S, Martinek V, Imhoff AB. Tissue engineering of the anterior cruciate ligament: a new method using acellularized tendon allografts and autologous fibroblasts. Arch Orthop Trauma Surg. 2007 May 31
2. Bhrany AD, Beckstead BL, Lang TC, Farwell DG, Giachelli CM, Ratner BD. Development of an esophagus acellular matrix tissue scaffold. Tissue Eng. 2006 Feb;12(2):319-30.

Imaging findings after meniscal repair with degradable polyurethane scaffold: preliminary results

P.C.M. Verdonk[1], R. Verdonk[1], W.C.J. Huysse[2], K.L. Verstraete[2]
1) Department of Orthopaedic Surgery, Ghent University Hospital, Belgium
2) Department of Radiology, Ghent University, Belgium

To date, there are no satisfactory solutions to the meniscal originated knee pain post meniscal tear repair. In this study a newly developed polyurethane material that has the intended properties of reducing pain and inducing tissue growth in a damaged meniscus is tested. Thus far 11 patients have received meniscal implants. Eight medial and three lateral menisci were operated. All implants covered the posterior horn with 3 reaching halfway into the meniscal body and one extending into the anterior horn. The average length of the scaffold meniscus measured on MR imaging was 45mm.

All patients will be imaged using conventional and dynamic MR imaging techniques at 1 week and 3, 12 and 24 months after surgery. The longest follow-up to date is 5 months. The influx of gadolinium contrast in a tissue during the first three minutes after injection gives a measure of the vascularisation, capillary permeability, perfusion and composition of the interstitial fluid. It can be measured using dynamic MRI and is represented as a Time Intensity Curve (TIC). This curve permits an evaluation of the healing process after surgery. In the first week after surgery, the capsule and suture area display fast and intense enhancement typical for post-operative inflammation and the formation of early scar-tissue. There is no enhancement in the base or the tip of the scaffold meniscus. After three months the speed and intensity of enhancement in the capsule and suture area between the remnants of the native meniscus and the scaffold have decreased indicating maturation of scar-tissue. However, the base of the scaffold meniscus now shows enhancement. This can only be explained by proliferation of blood vessels from the capsule and the residual meniscus wall into the scaffold meniscus. The tip of the matrix shows limited enhancement in some patients after three months.

On anatomical MR images, the signal intensity (SI) of the implanted scaffold is close to that of water on both T1- and T2-weighted spin echo and turbo spin echo sequences in the first week. After three months the SI decreases but is still clearly higher than that of the native meniscus. The implants in the posterior horn all had a normal position and no loosening of the sutures or tears of the scaffold were found. After three months, one of the patients had slight expulsion of body of the scaffold meniscus but this is a common finding in transplanted menisci.

DYNAMIC CONTACT MECHANICS OF A SCAFFOLD FOR PARTIAL MENISCAL REPLACEMENT

Robert H. Brophy, MD; Jocelyn Cottrell; Xiang-Hua Deng, MD; Scott A. Rodeo, MD; Timothy M. Wright, PhD; Suzanne A. Maher, PhD; **Russell F. Warren, MD**

Introduction/Background

Few options exist to reconstitute a meniscus after partial meniscectomy. Of the scaffolds being developed, little data exist on their ability to carry load – a key requirement of any meniscal substitute. The objective of this study was to develop a pre-clinical experimental model to measure the dynamic contact mechanics of a meniscal replacement. Our hypothesis was that partial meniscal replacement with a porous polyurethane scaffold (Orteq Ltd., United Kingdom) would restore the joint mechanics of the intact knee.

Materials & Methods

Six sheep cadaver knees were stripped of soft tissue except for the collateral and cruciate ligaments and the menisci. Each knee was potted using PMMA at 40º of flexion and aligned such that the epicondylar axis was collinear with the flexion/extension axis of rotation of a load-controlled knee simulator (Stanmore Model KC, University College London, Middlesex, UK). The simulator was programmed with a modified sheep gait profile - the knee was flexed through 35º, and axial compressive force peaked at 300 N. The AP force and axial torque loading profiles from the ISO standard for human gait (ISO #14243-1) were scaled to represent the average ovine body weight, and the simulator was run at 0.5 Hz.

Each cadaver was thawed prior to testing, and a Tekscan pressure sensor sheet (K-Scan-N, model 4010N, Tekscan Inc., South Boston, MA) was attached to the surface of the lateral tibial plateau using Tegaderm (3M, St. Paul, MN). Pressure data were recorded at 9.8 Hz for 10 gait cycles for the following conditions: (i) intact lateral meniscus, (ii) partial meniscectomy - where 50% of the AP length of the meniscus to within 1mm of the rim was removed, (iii) scaffold implantation – where the scaffold was sutured into the defect site, and (iv) total meniscectomy. For conditions (ii) through (iv), the LCL origin was taken down with a bony block to expose the meniscus, and re-attached using a screw and washer. Contact area, mean contact pressure, and peak contact pressure were calculated for each test condition. Peak contact pressure over the gait cycle was mapped for each knee. Data were analyzed using repeated measures ANOVA with post hoc contrasts.

Results

Average contact pressure (mean ± standard deviation) was: (i) intact, 0.71 ± 0.24 MPa; (ii) partial meniscectomy, 0.87 ± 0.13 MPa; (iii) scaffold, 0.71 ± 0.20 MPa; (iv) total meniscectomy, 2.6 ± 0.78 MPa. Peak contact pressure was: (i) intact, 2.16 ± 1.0 MPa; (ii) partial meniscectomy, 3.86 ± 1.32 MPa; (iv) scaffold, 2.95 ± 1.05 MPa; (iv) total meniscectomy, 4.69 ± 1.04 MPa. Contact area was: (i) intact, 279 ± 54 mm^2; (ii) partial meniscectomy, 184 ± 68 mm^2; (iii) scaffold, 222 ± 57mm^2; (iv) total meniscectomy, 57 ± 10 mm^2.

The average and peak contact pressures were significantly higher, and the contact areas were significantly smaller for the partial and total meniscectomy knees vs. the intact and scaffold implanted knees ($p \leq 0.005$). No significant difference was found between the average and peak contact pressures of the intact and scaffold implanted knees ($p \geq 0.99$). However, the contact area was significantly smaller for the scaffold implanted knees vs. intact knees ($p=0.005$).

The mean area in each knee exposed to peak pressure of at least 5 MPa during the gait cycle decreased from 12.7 mm^2 in the partial meniscectomy knee to 3.3 mm^2 in the scaffold knee ($p<0.05$).

Tissue Engineering approach for repair of Meniscal Defects in the avascular zone What is the best cell source?

Angele Peter, Zellner Johannes, Eichhorn Jürgen, Nerlich Michael
Department of Trauma Surgery, University Hospital Regensburg, Germany
angelepeter@aol.com

Introduction:
Meniscal lesions in the avascular zone are nowadays mainly treated by partial or subtotal meniscectomy, however this predisposes the knee joint for osteoarthritis. Tissue engineering provides a promising approach for the repair of these defects (1). However there is still the question for the best cell source for Tissue Engineering of meniscus.
Therefore the goal of this study was the evaluation of different cell sources (meniscal cells of the outer and inner zone, mesenchymal stem cells) for meniscus regeneration according to their chondrogenic differentiation potential and the biomechanical characteristics of the tissue engineered constructs. Furthermore in this study the healing response of avascular meniscal defects in degenerative knee joints of meniscal cell-matrix composites and mesenchymal stem cell-matrix composites should be analysed *in vivo*.

Material and Methods:
For the *in vitro* testing aggregates were cultured of human meniscal cells from the avascular and vascular zone (21 days). In the first seven days the aggregates were loaded with cyclic hydrostatic pressure (0,2-5 MPa, 1 Hz, 4h/d). The control groups were not loaded. Histological, immunhistochemical evaluation as well as DNA- and rt-PCR-analysis was performed on day 7, 14 and 21.
For the *in vivo* testing 2mm circular defects were inserted in the avascular zone of the lateral menisci in degenerative knee joints of adult New Zealand White Rabbits. Treatment as follows: *Group A*: defect filling with a hyaluronan-collagen composite matrix loaded with meniscal cells. The meniscal cells were harvested by a complete resection of both medial menisci of the rabbits and cultivated for 3 weeks prior to the seeding of the composite matrix and implantation *in vivo*. *Group B:* defect filling with a hyaluronan-collagen composite matrix loaded with mesenchymal progenitor cells, which were harvested from the iliac crest 3 weeks prior to the seeding of the composite matrix (2). After 6 and 12 weeks, all menisci of *groups A* and *B* were analysed macroscopically for stability and filling. Histological analysis for the quality of the surface area, integration, cellularity and cell morphology was also done. Immunohistochemistry for proteoglycan and collagen type II was done to characterise the repair tissue.

Results:
In vitro unloaded meniscal cells from the vascularised zone showed more chondrogenic potential than the unloaded avascular meniscal cells. For both cell types chondrogenesis was improved by cyclic hydrostatic loading, whereas fibrochondrocytes from the outer part of the meniscus showed an earlier incline of the collagen II content under biomechanical loading compared to meniscal cells from the inner part.
3 weeks after the resection of the medial menisci all the knee joints showed cartilage damage and degenerative aspects *in vivo*. The defects of *groups A and B,* which were treated with meniscal cell- and progenitor cell-matrix composites, were both completely filled with a stable meniscus-like tissue and the rupture was repaired. A positive proteoglycan and collagen II expression could be detected by histology and immunohistochemical analysis.
The healing response was analysed with the help of a developed macroscopic and histological based scoring system. The results showed no difference between the implantation of meniscal cell matrix composites (*group A*) and the implantation of progenitor cell-matrix composites (*group B*). In both cases the developed repair tissue had a high quality and was completely integrated in the surrounding native meniscus.

Discussion:
The chondrogenic potential of mesenchymal stem cells and their behaviour on mechanical loading is well described. The results of an earlier study (3), which focused on vascular/avascular defects, indicated that tissue–engineered cartilage with mesenchymal progenitor cells could be used to promote meniscal repair. This study shows that also meniscal cells from the outer and inner zone are possible cell sources for the repair of meniscal defects. Tissue engineering implants of hyaluronan-collagen composite matrices loaded with meniscal cells and mesenchymal stem cells both showed meniscal repair in the avascular zone by the development of a completely integrated meniscus-like repair tissue, even in degenerative knee joints. The therapy with meniscal cells as well as with mesenchymal stem cells showed good results, however the better availability and the potential to be modulated and differentiated *in vivo*, seems to be an advantage of the mesenchymal stem cells.

Literature:
(1) Angele P. et al. Tissue Eng. 5: 545 (1999)
(2) Johnstone B. et al. Exp Cell Res. 238: 265-272 (1998)
(3) Angele P. et al. J Biomed Mat Res (2007)

The reproducibility of radiographic measurement of lateral and medial meniscus horn position.

Wilmes P[1], Kohn D[1], Pape D[1], Seil R[2]

[1]University of Saarland, Department of Orthopaedics and Orthopaedic Surgery, Homburg/Saar

[2]Centre Hospitalier de Luxembourg, Department of Orthopaedic and Trauma Surgery, Luxembourg

Purpose: The objective of this investigation was to evaluate the possibility of locating and reproducing the tibial insertion areas of the anterior and posterior horns of the lateral and the medial meniscus on preoperative radiographs.

Methods: In 20 tibia heads, we prepared anterior and posterior horn insertions of both the lateral and the medial meniscus and marked their circumference with radiopaque steel balls of 1.6 mm in diameter. Standardized anteroposterior and lateral radiographs were made. On these radiographs, different landmarks were defined, their distances measured (tibial width and depth, distance from lateral tibia border to meniscus insertion midpoint, distance from anterior tibia border to meniscus insertion midpoint, distance from anterior and lateral tibia border to the lateral and the medial intercondylar spine) and ratios determined.

Results: For the lateral meniscus, anterior horn midpoint is located at 45.1 ± 1.3 % of tibial width and 41.9 ± 3.2 % of tibial depth, posterior horn midpoint at 49.8 % ± 1.9 % of tibial width and 72.1 ± 2.3 % of tibial depth. For the medial meniscus, anterior horn midpoint is located at 57.3 ± 2.7 % of tibial width and 12.0 ± 1.0 % of tibial depth, posterior horn midpoint at 56.5 % ± 1.6 % of tibial width and 81.6 ± 3.4 % of tibial depth. The statistical analysis of these measures showed a precise and constant positioning of the lateral and medial meniscus insertions on the tibia plateau. We found constant topographic relations between the lateral meniscus insertions and the lateral intercondylar spine as well as between the medial meniscus insertions and the medial intercondylar spine.

Conclusions: The anterior and posterior horn insertions of the lateral and the medial meniscus can be determined on radiographs with a high precision and reproducibility.

Clinical relevance: Development of a technique for precise radiographic tibial horn determination in lateral and medial meniscus transplantation.

Key words: lateral meniscus-medial meniscus-meniscus transplantation-meniscus insertion anatomy-bony landmarks.

Arthroscopic lateral Meniscal Allograft : Preliminary results at one year with clinical outcome and Arthro-MRI assessment.

V.Bongiorno, N.Solignac, N.Graveleau, N.Pujol, **Ph.Hardy**

Hôpital Ambroise Paré, Service d' Orthopédie, CHU
Paris Ile de France Ouest, 92100, Boulogne Billancourt

Summary:
Treatment of knee pain after Meniscectomy in a young patient is an actual therapeutic challenge.

Materials and methods:
Seven lateral Meniscal allograft were transplanted in seven patients (mean age 39,7, 18-52) between may 2005 and December 2006. All patients had already a lateral subtotal meniscectomy. All knees were stables (normal or previously reconstructed ACL); 2 knees had a normal alignment, 3 had a varus malalignment and 2 had a slight valgus malalignment. The meniscal allografts were cryoconserved, not irradiated. We prepared the grafts without bone-plugs, passing 2 sutures in any meniscal horn and 3 intermediate "vertical U" sutures. After removing of residual meniscal tissue we realized 2 tibial tunnels in the anatomic insertion area of the meniscal horns, then the allograft was inserted by an arthroscopic technique. All sutures were done by an outside-in technique. The posterior horn was stabilized by the means of a Fast-Fix device (1 to 5) in 3 patients. The mean follow-up was 12 months (23-93 months). We calculated an IKDC score for any patient. Schuss X-rays have been taken to evaluate the articular rim changes before and after the surgery. An arthro-MRI was performed at 6 months in order to evaluate the healing of the meniscal graft segments according to Henning's criteria, the position of the graft, the meniscal wall extrusion and the signal quality of the graft.

Results:
All patients were satisfied of the clinical and functional result at the follow-up control. The average post-operative subjective IKDC score was 57. The objective IKDC score was B in 3 patients, C in 3 patients and D in one. On the arthro-MRI control 6 meniscal grafts were considered as healed. The graft had a "normal" signal in 4 cases (compared to the medial meniscus) and a heterogeneous signal in 3 cases (on the T2 slides). Meniscal extrusion was less than 3 mm in 2 cases, and more than 5 mm in one case. Joint space height was stable in time. The functional result was better in the male patients that performed a high-level sport before.

Discussion and Conclusion:
Lateral meniscal allograft is a valid short-term therapeutic choice to treat post meniscectomy knee pain in young patients with a normal knee alignment and limited cartilage loss. The arthroscopic assisted technic is quite reliable without the limits of the traditional open surgery. A long-term follow-up is required to better evaluate these primary encouraging results.