Human meniscal transplantation

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The Meniscus

Once described as the functionless remains of leg muscle, the menisci are now realized to be one of the components in the complex biomechanics of the knee joint and to posses unique biomechanical properties. [1] In 1948 Fairbanks was the first to explain the phenomenon of early radiographic degenerative changes following total meniscectomy, which included flattening of the femoral condyles, ridge formation, and joint space narrowing. [2] Long-term follow-up of patients after total meniscectomy revealed a high incidence of abnormal physical findings and radiographic osteoarthritis. [3-5] The degree of degenerative change was proportional to the amount of meniscus removed. [6] These findings and the development of arthroscopic surgery has resulted in interest in the basic science of the meniscus.

Anatomy

Gross anatomy

Menisci are C-shaped disks of fibrocartilage. They are interposed between the tibial plateau and the femoral condyles. The peripheral border is thick and attached to the joint capsule. The innermost border tapers to a thin free edge. The proximal surfaces of the menisci are concave and in contact with the femoral condyles. The distal surfaces are flat and rest on the tibial plateau. The menisci thus serve to deepen the articular surface of the tibial plateau to accommodate better the femoral condyles. [1]

The semicircular medial meniscus is approximately 3.5 cm in length in anterior-posterior direction and is wider posteriorly than it is anteriorly. The anterior horn of the medial meniscus is attached to the tibial plateau in the anterior intercondylar fossa, in front of the anterior cruciate ligament (ACL). The posterior fibres of the anterior horn attachment merge with the transfers ligament, which connects the anterior horns of both medial and lateral menisci. The posterior horn

of the medial meniscus is attached to the posterior intercondylar fossa of the tibia between the attachments of the lateral meniscus and the posterior cruciate ligament. The periphery of the medial meniscus is attached to the joint capsule along the entire length of the meniscus. At its midpoint, the medial meniscus is more firmly attached to the femur and tibia through a condensation in the medial collateral ligament. [1]

The lateral meniscus is almost circular, covers a larger portion of the tibial plateau and is approximately the same width from front to back. The anterior horn of the lateral meniscus is attached to the tibia in front of the intercondylar eminence, behind the attachment of the ACL, with which it partially blends. The posterior horn of the lateral meniscus is attached behind the intercondylar eminence in front of the attachment of the posterior horn of the medial meniscus. There is no firm attachment to the lateral collateral ligament, but a loose peripheral attachment. The posterior horn of the lateral meniscus is also attached to the femur by means of the anterior and posterior meniscofemoral ligaments of Humphrey and Wrisberg, which originate near the origin of the posterior cruciate ligament. [1] Where the lateral meniscus is crossed by the popliteus tendon the peripheral edge of the meniscus is not attached to the capsule. The popliteus muscle arises not only from the femur but also has an attachment to the posterior edge of the lateral meniscus; this attachment shows great variation in size and may be small or relatively large. [7]

Microanatomy and Biochemistry

The microanatomy of the meniscus is complex and age-dependent.
Menisci are composed of fibrocartilaginous tissue consisting of water (75%), collagen fibers (20%) and a small amount of proteoglycans and cells. [8, 9]

The extracellular matrix is made up mainly of collagen, with smaller quantities of proteoglycans, matrix glycoproteins and elastin. The fibers consists mainly of type 1 collagen (90%), with smaller quantities (10%) of type 2,3,5 collagen. [9] The type 1 collagen fibers are orientated predominantly in a circumferential direction, making the meniscus much stiffer in the circumference than in radial direction. [10, 11] Some fibers run in radial direction and are named radial tie fibres. The number and size of the radial tie fibers increase from the anterior region to the posterior region. In the posterior region the radial tie fibers form a sheet, increasing tensile modulus and ultimate tensile stress, making the posterior region more stiff. Skaggs et al concluded that a structure-function relationship is illustrated by the regional variation in both the ultrastructure of the radial tie fibers and the radial tensile properties. [11] The fibrocartilage matrix is synthesised by fibrochondrocytes, the cells of the meniscus. Two morphological populations of fibrochon-

drocytes can be distinguished. In the superficial zone the cells are oval and fusiform with relatively little cytoplasma and organelles. In the deeper zone the cells are rounded and have prominent rough endoplasmatic reticulum and golgi complex. [9, 12]

Biochemically the normal meniscus contains 0.10-0.12% DNA, 70-75% water, 20-22% collagen and 0.6-0.8% total glycosaminoglycans (GAG). 40% of GAG's are chondroitin-6-sulphate, 20% chondroitin-4-sulphate, 20% dermatan-sulphate, 15% keratin-sulphate, and 3% hyaluronate. [13] The biochemical structure of the extracellular matrix is not uniformly divided over the meniscus. The ligamentous horns which are subjected to tensile forces contain more dermatan-sulphate than the meniscus body, which is subjected to axially loaded compressive forces as well as tensile forces. The meniscus body is hyalinized and contains more chondroitin-sulphates. [14]

There are differences between species. The dermatan-sulphate richer human meniscus body is grossly and histologically more fibrous and stains less well with Safranin-O than the dermatan-sulphate poorer canine meniscus body. In porcine menisci the extracellular matrix varies across its width, consistent with the general principle that composition in connective tissue reflects function, with increased compressive loading of the thinner, inside aspect of the meniscus. The innermost zone consisted of approximately 76% collagen by dry weight and approximately 8% GAG. For the outermost zone the values are 93% and 2%, respectively. The innermost zone had results between those for the inner and outer zones. There were no significant biochemical differences between medial and lateral menisci. [15]

In conclusion, the proportions of collagen and GAG varies inversely across the meniscus, with the highest concentrations of GAG's and the lowest concentrations of collagen inside. [16]

Vascular anatomy

Arnoczky and Warren demonstrated that the meniscus blood supply originates from the superior and inferior branches of the lateral and medial genicular arteries. [17] These vessels give rise to a perimeniscal capillary plexus, within the synovial and capsular tissues of the knee joint. This plexus supplies the peripheral border of the meniscus about its attachment to the joint capsule. These perimeniscal vessels are in a circumferential pattern, with radial branches directed toward the center of the joint. It was shown that the degree of peripheral vascular penetration is 10 - 30% of the width of the medial meniscus and 10 - 25% of the width of the lateral meniscus. [17] Day et al confirmed that the vascular supply is limited to the outer one-third of the meniscus. [18]

Clark and Ogden demonstrated that the prenatal menisci are very cellular

and have numerous intrameniscal vessels. [10] After birth a gradual change in vascularisation occurs, which includes a decreasing vascularity from the central to the peripheral margin of the meniscus. [18]

The middle genicular artery also supplies vessels to the menisci through the vascular synovial covering of the anterior and posterior horn attachments. These synovial vessels enter the meniscal horns and end in terminal capillary loops. [17]

On both the femoral and tibial articular meniscal surfaces, vascular synovial tissue is present throughout the peripheral attachment of the medial and lateral meniscus. This "synovial fringe" extends over a short distance (1-1,5 mm), and contains small vessels which anastomose with one another. It is intimately adherent to the articular surfaces of the menisci, but does not contribute vessels to the meniscus per se. [17, 19] The synovial fringe has an important role in healing of the meniscus. [19]

The avascular part , the vast majority of the meniscus, derives its nourishment from diffusion and mechanical pumping (i.e. compression during motion). Due to the dense fibrous, extracellular matrix, diffusion into the central core of the meniscus may be marginal. On the articular surfaces, the presence of openings (10-200 um in diameter) were shown in human and animal menisci. The canal system could provide a mechanism through which a transudate of serum could pass, and thus supply nutrients to the cells throughout the meniscus. [1, 20]

Neuroanatomy

Neural elements have been identified in the human meniscus. [18, 21-23] The nerve supply to the meniscal horns is greater than that of the body, but nerves are also seen in the interstitial tissue of the outer one-third of the meniscal body. The neural network extends from the richly innervated perimeniscal connective tissue and radiates into the outer and middle thirds of the meniscus. Most nerves are closely associated with the vascular network. [18, 21, 23] Receptors are seen in the perimeniscal connective tissue and within the meniscus itself. Three distinct mechanoreceptors have been identified; Ruffini endings, Golgi tendon organs and Pacinian corpuscules. [18, 23] Theoretically these neuroreceptors could play an afferent role in propriocepsis. And the greater the concentration of nerves found in the mensical horns is due to the need for afferent feedback of flexion and extension.[23]

Biomechanical Function of the Meniscus

Function of the meniscus

Basic research has shown that intact menisci are necessary for normal knee joint function. The menisci have an important role in load transmission, shock absorption, joint stability, lubrication and nourishment of articular cartilage, and they

play a role in propriocepsis. [18, 24-27] Both menisci transmit at least 50% of the compressive load on the joint in the flexion range of 0° - 90°. [28] The load-distribution function of the menisci are directly corroborated by comparing the results obtained after meniscectomy to those measured in intact joints. When loaded in vitro, 70 % and 50 % of the loads in the lateral and medial compartments of the knee joint are transmitted through the corresponding menisci. After meniscectomy the contact area between menisci and articular cartilage is reduced which leads to increased peak stress and stress concentration on articular cartilage of the femur and tibia, and decreased shock absorption. [28] Different clinical studies showed that meniscectomy leads to degenerative changes in the knee joint. [2, 4, 5, 29, 30] Partial meniscectomy has less detrimental effect than total meniscectomy. Degenerative changes after meniscectomy are directly proportional to the amount of tissue removed. [6, 31]

Because of the greater role in stress protection of the lateral meniscus compared to the medial meniscus, lateral meniscectomy will be followed by a higher incidence of osteoarthritis. [5, 32, 33] Hoser et al. found that although early results of arthroscopic partial lateral meniscectomy may be satisfactory, in the long term, a mean follow-up of 10 years, there was a high incidence of degenerative changes, a high rate of re-operation and a relative low functional outcome. [34] These findings were confirmed by McNicholas et al in a study with 30-years follow-up after total meniscectomy in adolescence. They found that the outcome measures were best after total medial, intermediate after lateral and worst after double meniscectomy. [35]

The menisci are not primary stabilisers of the knee joint, but in ligament insufficient knees they assist in joint stability. Levy et al found that isolated excision of the medial meniscus had little effect on the forced anterior-posterior displacement of the tibia on the femur. However, when medial meniscectomy followed section of the ACL, the displacement was increased significantly at all flexion angles. The greatest increase was at 90° of flexion, the smallest at full extension. Posterior displacement in knees with combined medial meniscectomy and section of the ACL was not different from that of the intact knee at all angles of flexion. [36] This demonstrated that the medial meniscus is a secondary restraint to anterior tibial translation in the ACL-deficient knee.

Considering rotations in the knee joint it has been demonstrated that an anteriorly directed force produced not only an anterior translation of the tibia but also a coupled internal rotation. [37] Medial meniscectomy had no effect on the coupled internal tibial rotation and anterior translation. [36] The coupled internal rotation and anterior translation was lost after section of the ACL, but not influenced by medial meniscectomy. [36, 37]

In addition, the medial meniscus has not only been shown to enhance stability under anterior-posterior, but also under varus-valgus, and internal-external rotation load when the ACL is absent. [38, 39] Allen et al. demonstrated that the medial meniscus sustains an increase in anterior-posterior load sharing in ACL-deficient knees. [40] This biomechanical interdependence between the ACL and the medial meniscus was confirmed in two studies. Both Hollis et al. and Papageorgiou et al. demonstrated that anterior tibial translation and medial meniscal strain were restored to a level similar in normal knees after reconstruction of the ACL. [41, 42]

After resection of the lateral meniscus, the amount of anterior and posterior translation was unchanged compared to the intact knee. Isolated section of the ACL resulted in significant increases in anterior translation at all angles of flexion. Primary anterior and posterior translations were not affected by lateral meniscectomy before or after resection of the ACL. [43]

Briefly, in deficiency of the ACL, the medial meniscus is of more importance to stability than the lateral meniscus. Whereas the lateral meniscus is of more importance to load-transmission than the medial meniscus.

The contribution of the menisci to varus-valgus stability in unloaded and loaded knees was tested by Markolf et al. After medial and lateral meniscectomy in fully extended unloaded knees, anterior-posterior neutral stiffness and varus-valgus *neutral stiffness were reduced, varus-valgus laxity, and varus-valgus rotation was* increased significantly. [44]

The shock absorption function is illustrated as follows; during heel strike, impact generates a stress wave that propagates through the tibia and the knee joint. The meniscus attenuates these stress waves by as much as 20%. [45]

The knee is able to move at a wide range of rates in the presence of large forces with a minimal friction between the contact surfaces. This results in a variety of lubrication mechanisms to which the meniscus contributes significantly. The entrapped water in the meniscus makes up 75% of the total weight. Under compression, much fluid extrudes into the joint space, increasing the available fluid lubricant. This phenomenon is called weeping lubrication. Removal of the meniscus decreases the effectiveness of this process, which may contribute to the degenerative process. [45]

Composition and mechanical properties of the meniscus

The meniscus consists of collagen, proteoglycans and meniscal fibrochondrocytes.

Collagen is the largest component of the meniscus. The mechanical properties of collagen fibers are their tensile stiffness and strength. These fibrils are aligned along the direction of the largest tensile stress. During loading, radial

(extrusive) forces are resisted by the firm attachments to the tibia at the anterior and posterior horns. This produces large circumferential orientated hoop tensile stress, which tends to reflect the local tensile stresses within the meniscus. [45]

The proteoglycans provide the tissue with a high capacity to resist compressive forces. The overall proteoglycan content is 3% of the dry weight, but varies with age. The quantitatively major proteoglycans present consist of an extended protein core to which many chondroitin- and keratin-sulphate chains are attached. Each proteoglycan-hyaluronate bond is stabilised by a link protein. These aggregating proteoglycans contribute most significantly to the material properties of cartilage. The function of aggregation appears to be to immobilise the proteoglycans within the collagen network. [27] The chondroitin-sulphate and keratin-sulphate chains of the proteoglycans are composed of repeating disacharide units, which charge the interstitium. Therefore a high concentration of counter-ions (Na+) is required to maintain electroneutrality. The concentration of the counterions is the source of the interstitial osmotic pressure, the Donnan osmotic pressure. The fixed negative charges also develop strong charge-to-charge repulsive forces along the proteoglycans, which extends the proteoglycan molecule. These characteristics of proteoglycans endow meniscal cartilage with the following properties; compressive stiffness, tissue hydration and swelling, low permeability, and shear stiffness. [27]

The degree of hydratation in cartilaginous tissue depends on the swelling pressure, which is the sum of the Donnan osmotic pressure and the charge-to-charge repulsion forces, and tensile stiffness of the restraining collagen meshwork surrounding the trapped proteoglycans. Tissue with a high proteoglycan / collagen ratio tends to swell more than tissue with a low ratio. In degenerated tissue the collagen meshwork is damaged. The effect is loss of proteoglycans, and thus a reduction of the swelling effects. The space, vacated by the proteoglycans in the interfibrillar space, will be filled by water. Therefore in damaged collagen the tissue will gain more water than normal. Collagen and proteoglycan damage may be caused by mechanical factors, by enzymatic activity, or by the synthesis of new, poorly functioning molecules. When collagen is weakened or damaged, tissue changes are mostly irreversible. When proteoglycans are damaged and lost within the intact the collagen network, the changes are often reversible. This occurs, for example, after joint immobilisation or unloading. [27]

The collagen-collagen cross-links are covalent bindings. They provide cohesion and strength for the collagen meshwork and immobilise the collagen fibrils. Noncovalent bindings are mechanical entanglements, and electrostatic interactions like the proteoglycan-proteoglycan and collagen-proteoglycan bindings. Electrostatic interactions can be influenced by counter-ion concentrations in the

interstitium. These ion concentration changes have been shown to alter the tensile, compressive and swelling properties of cartilage. When salt concentration is decreased or increased, the tensile and compressive moduli increase and decrease, respectively. [27]

Cells and Cellular activity: The fibrochondrocytes are responsible for the synthesis, maintenance and normal repair of the extracellular matrix. Little is known about meniscal fibrochondrocytes, most research is derived from articular cartilage, tendons and ligaments. In vitro experiments have shown that metabolic activities are influenced by hydrostatic pressure and mechanical loading. It is suggested that cell deformation may be an essential signal to modulate proteoglycan synthesis. [27]

Mechanical properties of the meniscus

The meniscus possesses a complex set of material properties, resulting in different deformational behaviour in tension, compression and shear. The deformational behaviour is inhomogenous and anisotropic. Briefly, the ultrastructure is composed of collagen fibrils arranged circumferentially with radial tie fibers in which the proteoglycans are immobilised and form large aggregates.

Mechanically, the matrix is a biphasic composite. The solid phase (26% total weight) consists of collagen, proteoglycans and non-collagenous proteins. The fluid phase (74% total weight) consists of water and interstitial electrolytes. Most of the fluid phase is forced through the porous-permeable matrix by a hydrolytic pressure gradient and matrix compression. [27, 45]

Compressive forces in the knee generate tensile stresses in the meniscus. Tensile testing revealed that the circumferential collagen fibers from the femoral surface appeared to be isotropic, whereas those of the deeper zones were anisotropic. The areas containing radial tie fibers had a higher tensile stiffness, and serve to decrease the amount of shear forces. The variation in the tensile stiffness and strength of the menisci appeared to reflect local differences in collagen ultrastructure and perhaps intermolecular interactions are the predominant factors influencing the inhomogeneity in tensile responses of the meniscus. The organisation of both radial and circumferential fibers within the matrix may thus be an important factor in the aetiology of meniscal tears. [27]

When a joint is loaded over a long period of time, the contact area gradually increases as a result of creep, spreading the compressive force over a larger area, and thus reducing the stress. Stress relaxation makes it difficult to maintain high forces in the collagen-proteoglycan solid matrix for extended periods of time. Stress may reach high levels momentarily, but interstitial fluid redistribution will always occur to decrease the tissue stress with time. The related creep and stress-

relaxation are important in the load distribution and shock absorption function of the meniscus. [45]

The mechanical functions of the menisci are determined not only by their material properties and shape, but also their anatomical attachments, the shapes of the femoral and tibial condyles, as well as the magnitude and direction of the force applied to the knee. An accurate model of the knee must include all these factors. Mow et al believe that a more accurate model is needed. It is demonstrated that a linear elastic material is not representative for the meniscus. The finite element models must not only consider the biphasic nature, but also the anisotropies and inhomogeneities of the tissue. Since the anatomical shape reduces the geometric incongruities between tibial plateau and femoral condyles, 3-D knowledge of the surface geometry of the meniscus and femoral condyles must also be included. [27]

Meniscus Movement

Biomechanically the human knee joint can be described as having six degrees of freedom. The possible translations along the three orthogonal axes include anterior-posterior, medial-lateral, and proximal-distal translation. The corresponding translations are varus-valgus, flexion-extension, and internal-external rotation, respectively. [46] Blankevoort et al concluded that reproducible finite helical axes can be found for passive knee-joint motions. For internal and external motion pathways, the axes are relative to all anatomical planes and reflect the combined occurrence of flexion and axial rotation. The axes move posteriorly above 70° of flexion. The helical translations are relatively small, but indicate a medial translation of the tibia relative to the femur with increasing flexion. [47]

Although the knee-joint is not a simple hinge, the primal movement is flexion-extension and consists of a varying mixture of rolling and gliding. The ratio of rolling and gliding changes throughout flexion. During early flexion the femoral condyles demonstrate rolling predominantly. The gliding component increases during flexion so that the femoral condyl glide on the tibial plateau at full flexion. [48] The overall rolling to gliding ratio for the medial condyle was 1:1 and 1:4 for the lateral condylé. [49]

In general, meniscus movement will be influenced by the capsular, muscular and ligamentous attachments and by the bony geometry of lateral and medial condyles and the tibial plateau. In a cadaver study meniscal movement was evaluated using MR imaging and 3-D reconstruction technique. Each knee was examined sagitally at 10 degree increments of knee flexion from 0 to 120°, in a non-weight-bearing situation. The mean medial meniscal movement was 5.1 ± 0,96 mm and the mean lateral meniscal movement was 11.2 ± 3.27 mm. The ratio of medial to lateral movement was 1:2.3±0.86, and was statistically significant.

Segmental analysis of both menisci showed less displacement of the posterior horns compared to the anterior horns with flexion, most markedly in the posterior medial corner. The anterior horns were in general less restricted. [50] Vedi et al studied meniscal movement in an open MR scanner, in vivo, in young football-players. The knee joint was scanned moving from full extension to 90° of flexion in the sagital and coronal planes, and in weight-bearing and non-weight-bearing positions. They showed meniscal movement through the arc of flexion to be clearly evident in both the sagital and coronal planes. The study confirmed that the anterior horn movement was greater than the posterior horn movement. Radial displacement during flexion was the same for the lateral and medial meniscus. Concerning weight-bearing, they concluded that the movement of the lateral meniscus was greater when the knee was loaded. [51] Both studies confirmed that the menisci remained in constant contact with both the tibial and femoral articular surfaces throughout the arc of flexion. [50, 51] Knee motion during rotations demonstrated greater rotational effects of the lateral compartment compared to the medial compartment. This greater lateral displacement is also reflected by the menisci. [52]

Concerning deformation of the meniscus, the anterior horn of the medial meniscus showed most deformation due to increasing load resulting from knee flexion. [50] According to Vedi et al, there appeared to be a difference in the change of height of the anterior horn of the lateral meniscus between weight-bearing and non-weight-bearing. But there was no statistically significant difference between meniscal movements in loaded and unloaded knees. [51]

In conclusion, the marked mobility of the lateral meniscus and the limited motion in the posterior medial corner explains the decreased risk of lateral to a medial meniscal injuries. Because meniscal movement ensures maximal congruency with articular surfaces during flexion, load transmission, stability and lubrication are facilitated. This phenomenon can be defined as dynamic congruency.

Meniscal pathology

Meniscal tears

Injury of the menisci is common in young active individuals through contact and non-contact mechanisms. Direct contact with the knee is less common and is associated with other injuries, mostly rupture of the ACL, or tibial plateau fractures. Non-contact meniscal injuries are the results of rapid changes in velocity or axial rotation in a loaded knee, or a combination of squatting and twisting movements. Soccer, track and field, and downhill skiing are the most common sources of meniscal injuries in athletes. Related to profession meniscal injuries occur frequently in miners, electricians and road-menders. Lesions in the medial meniscus

occur three times more frequently than those of the lateral meniscus. Longitudinal, vertical tears, that run anteroir-posteriorly, are the most common. Extension of this type of tear can produce a bucket handle lesion. Transverse vertical tears are much less frequent, mostly located in the middle third of the meniscus and can extend in radial direction, becoming a flap tear. [45]

Meniscal injuries can occur in stable and in ligament-deficient knees. The incidence of concomitant meniscal tears in patients with an acute tear of the ACL vary between 19% to 76%, increasing to 53% to 100% in patients with chronic instability of the ACL. [53-56] In the study by Keene it was demonstrated that with the increasing incidence of meniscal injury in chronic ACL-deficient knees, the meniscal tears became more complex and therefore less amendable to repair. [56]

Aging effect on menisci

A degenerative meniscus tear is more common in patients over the age of 40 years. A degenerative tear can occur spontaneously and frequently produces horizontal cleavage tears. [45] Egner gave a description of the development of degenerative changes in meniscal tissue. [57] The first signs of spontaneous degeneration were found in the fibrochondrocytes, showing nuclear pycnosis, karyolysis and karyorrhexis as indicators of irreversible cell damage. Mechanical resistance is impaired, characterised by progressive fragmentation of collagen fibers, most intensely in oblique and transverse fibers, whereas the longitudinal fibers were only mildly and later affected during the degeneration process. [57] Herwig et al found that the water content of the menisci was correlated with the grade of degeneration. They also found a decrease of the collagen content of the wet weight of tissue in relation to degeneration. But this was not detectable when collagen concentration was expressed per dry weight unit of tissue. The GAG's content of the dry weight of menisci, however, tended to increase, thus giving evidence for accumulation of water binding proteoglycans in degenerated menisci. [13] They did not find a correlation between the degree of degeneration versus the age of the patient. Ghosh and Taylor concluded that the collagen content of the normal meniscus increased from birth to 30 years, than remained constant until 80 years of age, after which it declined. [58] In contrast, the non-collagenous matrix proteins decreased till 30 years of age, was steady till 70 years and increased after 70 years of age. [59] Others found that aging of the meniscus was associated with an increased ratio of chondroitin-6-sulphate to chondroitin-4-sulphate and keratin-sulphate to chondroitin-sulphate. [60]

Meniscal regeneration, healing and repair

Regeneration

Meniscal regeneration is still controversial. Experiments in rabbits showed a higher incidence of meniscal regeneration after medial than after lateral meniscectomy. Complete medial meniscal regeneration was found in 23% of 44 medial meniscectomy knees, partial regeneration in 68%, and no regeneration in 9%. Among 44 lateral meniscectomies, only 5% had complete meniscal regeneration, and 68% had no meniscal regeneration. The remaining 27% of knees had partial regeneration. [61] In only one study in humans it was shown that 10 years after total meniscectomy regeneration of a meniscus-like structure occurred. This meniscus-like structure had a radius of one-third of a normal meniscus. [62] After synovectomy, which removes the synovial fringe, no regeneration of the meniscus took place. Thus, both the synovial fringe and the peripheral meniscal vascularisation contribute to the regenerative process.

Although meniscal regeneration occurs only after total meniscectomy, a remodelling response had been observed in the avascular part of the meniscus after partial meniscectomy. This occurred only in 67% of the menisci, probably by an extrinsic factor, which is still unknown. [63, 72]

Healing and repair

In 1936 King demonstrated in his study in dogs that meniscal lesions could heal spontaneously, provided that the lesion was located in the peripheral vascular zone. [64] After injury of a meniscus in the peripheral zone, a fibrin clot is formed. This fibrin clot is rich in inflammatory response cells. These inflammatory cells induce the proliferation of vessels. The vessels proliferate from the perimeniscal capillary plexus and the synovial fringe, and penetrate through the fibrin clot with undifferentiated mesenchymal cells. The lesion is filled with fibrovascular scar tissue that glues the wound edge and appears continuous with the normal meniscal tissue. Later in the healing process, a vascular pannus appears over the area of the scar tissue extending the synovial tissue. After months the scar is modulated to normal appearing meniscal fibrocartilage. [19]

Based on the healing process described by Arnoczky and Warren the technique of meniscus suturing has been developed with promising results. Meniscal suturing is only indicated in tears in the red-red and red-white zone. A red-red tear means a peripheral detachment, a red-white tear means a tear through the peripheral vascular zone. [65-69] Tears of the avascular zone, white-white zone, are incapable of healing and therefore partial meniscectomy is advised. To extend the healing process to the avascular zone experimental techniques have been developed. Examples of these experiments are; the creation of vascular access channels, syn-

ovial pedicle flaps, synovial abrasion, exogen fibrin clot, induced neovascularisation by angionin, and porous polymer implants. [19, 70-75] The quality of the scar tissue and the results are still being discussed.

Indications for meniscal repair are longitudinal lesions within the vascular part of the meniscus. Contra-indications include stable longitudinal tears shorter than 1 cm, partial thickness tears, degenerative tears and joint instability. If meniscal repair is possible in a knee with deficiency of the ACL, it should be done in conjunction with an ACL-reconstruction. [69]

Meniscal repair is described as an open- and an arthroscopic technique. [76, 77] Different arthroscopic suturing techniques have been described; inside-out, outside-in, all-inside, all with satisfactory results and meniscal repair is considered an advance in meniscal sparing therapy. [69,78-85] Various studies of midterm results (less than 10 years of follow-up) have reported success rates of meniscal repair to vary from 63% to 91%. [86] There are three recent studies of meniscal repair with a follow-up of more than 10 years. Rockborn and Gillquist showed, in their series of open meniscal repair in stable knees, a failure rate of 29% after 13 years, with near normal function and no significant difference in radiological changes between the repair and the control group. [87] In another study the clinical and MRI findings after open meniscal repair demonstrated a survival rate of 91% after twelve years. [88] After an average follow-up of 10 years arthroscopic inside-out meniscal repair indicated a clinical success rate of 76%. [89] To my knowledge no long-term results of the outside-in technique are described. Both the inside-out and the outside-in techniques have advantages and disadvantages. Van Trommel et al recommended the inside-out technique for the posterior regions and the outside-in technique for the anterior regions of the menisci. [90]

The success rates of meniscal repair are influenced by several factors including rim width,deficiency of the ACL, concomitant reconstruction of the ACL, tear length, and whether the tear is acute or chronic. The most important factors seem to be the rim width, the distance of the tear from the meniscosynovial junction. [86] Deficiency of the ACL has a significant impact on the results of meniscal repair. No distinction is made between lateral or medial meniscal repairs. Because of differences in anatomy and biomechanical functions of the lateral to the medial meniscus, better results could be expected for lateral meniscal repairs in ACL-deficient knees than for the medial repairs.

Factors that do not seem to affect the healing rates include age and open or arthroscopic repair. [86] Whether the latter also include arthroscopic all-inside technique is not clear.

For the open, and arthroscopic inside-out and outside-in techniques mostly absorbable sutures are used. For the arthroscopic all-inside technique different

absorbable devices have been developed. In a study testing the pull-out strength of vertical and horizontal loop sutures and absorbable arrows it was shown that the vertical loop sutures had the highest pull-out strength, followed by the horizontal loop sutures. The biogradable meniscal repair device had the least pul-out strength. [91] A second aspect in favour of the sutures is the cost. The repair devices are more expensive than the absorbable sutures.

Complications after open and arthroscopic repair include superficial and deep infection, deep venous thrombosis, arthrofibrosis and complex regional pain syndrome. Before the use of posterior incisions was recommended in meniscal repair, to protect the neurovascular structures, major procedure-specific complications were encountered, including nerve injuries laterally, saphenous nerve injuries medially and popliteal artery injuries requiring vascular reconstruction and amputation. The posterior incisions have been documented to greatly reduce the risk of these serious complications. [86] The arthroscopic all-inside technique has device-specific complications, including subcutaneous migration, aseptic synovitis and chondral lesions because of the biogradable device. [92-95]

Nevertheless, most meniscal lesions occur in the avascular zone. The indication for meniscal repair is therefore limited and arthroscopic partial meniscectomy is the treatment of choice. The clinical results of partial meniscectomy are generally good, and favourable to total meniscectomy. Particularly in patients older than 40 years of age the results are acceptable and effective in the long-term. [96]

Meniscal Replacement

Experiments in meniscal reconstruction

Studies to substitute or reconstruct the menisci with a teflon-net, carbon fiber-polyurethane grafts, copolymeric collagen scaffolds, tendon autografts and fatpads are described, but still experimental. [97-101] These techniques are based on the phenomenon of creeping substitution. The scaffold forms a meshwork in which vessels and cells penetrate. From the perimeniscal capillary plexus and the vascular fringe vessels will proliferate into the scaffold together with mesenchymal cells which will remodel into a new meniscus matrix. The scaffold has the function of a porous meniscal prosthesis.

Prerequisites for a meniscal prosthesis are biocompatibility, e.g. will not give rise to a foreign-body reaction, or synovitis due to particle wear. Biogradable materials should be used. Solvability should be in balance with the growth of new meniscal tissue. It should have the same biomechanical properties as meniscal tissue. The prosthesis should gain the normal contour of a meniscus as soon as possible in order to be congruent to femoral and tibial condyles. And the prosthesis should not give rise to degeneration of the joint. Clinically the effect of the pros-

thesis should be a decrease in pain. Nevertheless, the concept of a prosthetic meniscal replacement has been abandoned in the experimental phase.

Experiments with meniscal transplantations

After total meniscectomy meniscal transplantation is an alternative to replace the meniscus. In animals menisci have been transplanted in merino sheep, dogs and goats. [102-106] In humans meniscal transplantations have been performed with or without additional procedures. [102, 107-111] The results of these meniscal transplantations showed that the transplanted menisci were firmly attached to the knee capsule by fibrovascular tissue, without signs of an inflammatory response or rejection. [102-104] Although no cellular and humoral responses to fresh meniscal allografts in mice were found, a minimal lymphocyte invasion into the allogeneic meniscus was observed. [112] Serological HLA typing in humans after meniscal transplantation showed that 11 of 18 recipients became sensitized. [113] Histological evidence of an subtle immune response directed against the the allograft was shown, but again this response does not appear to affect the clinical outcome. [114] This subtle immune response probably evokes the phenomenon of creeping substitution of the meniscal allograft. If creeping substitution takes place than incorporation, revascularisation and cellular repopulation of the allograft must occur. Evidence of this phenomenon is given because recipient DNA material has been

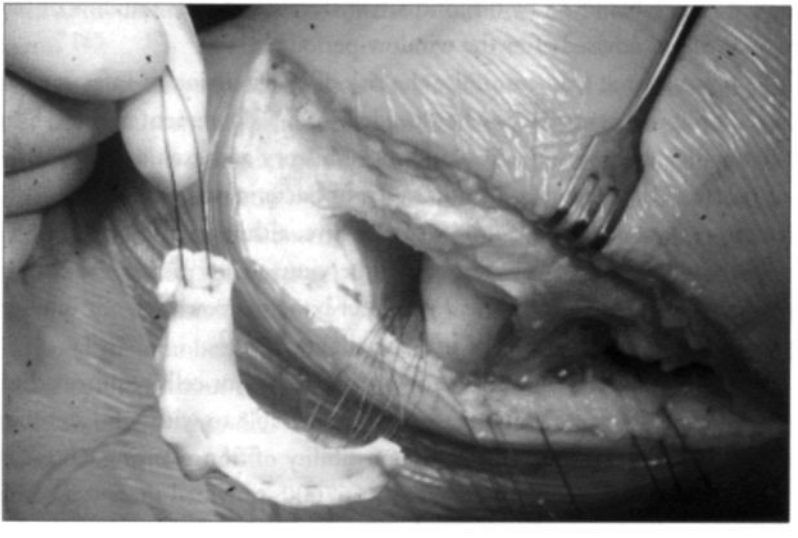

Fig 1. Meniscal transplantation; under direct vison all the sutures are pulled through the capsule, no bone blocks are used to fix the allograft.

found in biopsy material of transplanted meniscal allografts. [115, 116] But the statement of Debeer et al that repopulation is nearly completed 1 year after transplantation of the allograft seems to be a little too optimistic. This conclusion can be made only after a complete analysis of the allograft and not after analysis of biopsy specimens.

Mensical transplantation; the Donor side

Transplanting menisci includes a potential risk of infectious disease transmission through the allograft.

In blood transfusion it is known that many transfusion-transmissible viruses are found at higher rates in paid than in volunteer donors, and patients receiving blood from volunteers have fewer transfusion-transmitted infections. [117] Therefore the United States and Europe converted from paid blood donors to totally voluntary, nonremunerated donor sources for blood donation. The World Health Assembly condemned payment of blood donors as "exploitation of the poor".

Transplantation of organs, tissue and cells has resulted in transmitting, bacterial, viral and fungal diseases from donor to recipient. [118] Simonds et al reported about a male donor who died 32 hours after a gunshot wound; he had no risk factors for HIV-1 infection and was seronegative. Of the 48 recipients who obtained tissues and organs from this donor, all four recipients of organs and three recipients of unprocessed fresh-frozen bone were infected with HIV-1. [119] It is generally accepted that after HIV exposure, 95% of the individuals will have HIV antibody at detectable levels by 6 months. [120] Because of this "window of seronegativity" retesting is advised after the window-period. [121]

To prevent or at least minimise the risk of transmission of infectious disease one should only use transplants when needed. The procurement agency should carefully obtain the donor's medical and social history and exclude those suspected to be at risk for HIV, hepatitis, or other viral or bacterial infections. [118] Sterilization of certain tissues can be very effective, although some infectious agents, like Creutzfeld Jacobs Disease are impervious to sterilizants. Nemsek et al showed that routine processing and removal of bone marrow may not inhibit the ability to transmit viruses like HIV in bone allografts. [122]

The clinical effectiveness of many organs, tissues or cells requires cellular viability. Like meniscal allografts, these grafts are unable to withstand sterilization procedures. Buck et al estimated that the possibility of transplanting a bone allograft from a donor infected with HIV is 1/1667600, provided there is a combination of rigorous donor selection, screening for the HIV antigen and antibody, and histopathological studies of donor tissues. If adequate precautions are not taken the risk might be as high as one in 161. [123]

In conclusion, donor selection is an important factor. Donors should meet the criteria of the American Association of Tissue Banks or the standards of the European Association of Tissue Banks and the European Association of Musculo Skeletal Transplantation in order to prevent transmission of diseases. Procurement should be done under aseptic conditions in an operating room.

Different banking techniques have been developed. Donor menisci could be banked fresh, frozen, or cryopreserved. Prerequisites for human meniscal allografts are viability of meniscal fibrochondrocytes after preservation and transplantation, and an intact collagen matrix in the long-term to maintain the meniscal biomechanical function. Fresh meniscal preservation offers a source of living chondrocytes. A disadvantage of fresh preservation techniques is that transplantation has to be performed within 48 hours after procurement which necessitates an expensive organisation, and patients on call.

Concerning frozen meniscal allografts, no considerations are made to preserve cell viability. Storage, preservation and tawning is relatively easy. After transplantation of deep-frozen autografts in dogs, cellular repopulation was noted. [124] However Milachowski et al noted severe shrinkage after deep-frozen meniscal allografts in humans. [102] Although in dogs repopulation of cells was noted a general statement in transplant surgery is that it does not seem to be appropriate to implant organs or tissue of which the cells are for the most part irreversibly damaged. The time span in which the cellular population of the organ or tissue could be held before the point of no return of irreversible damage, at low temperature and optimal medium, is significant for the possibilities and limitations of a transplantation. [125]

The cryopreservation technique has the advantage of being a source of living cells, and meniscal transplantation could be performed under elective circumstances, without extra overhead costs. As cryopreservent glycerol or dimethylsulphoxide (DSMO) are used. [73, 126] Although cryopreservation and short-term storage do not appear to have an effect on the morphological appearance or the biomechanical character of the meniscus, only reduced numbers of the fibrochondrocytes were metabolically active. [104] Ohlendorf et al. showed that cryopreservation increased the numbers of surviving cells compared to cell survival in osteochondral allograft without cryopreservation. They also provided evidence that cryopreservation of osteochondral allografts was confined to the cells in the superficial layer of the cartilage. [127]

Meniscal transplantation, Technical aspects

When meniscal transplantation is indicated there are some prerequisites;

1. The donor should meet the criteria of the American Association of Tissue

Banks or the standards of the European Association of Tissue Banks and the European Association of Musculo Skeletal Transplantation, and procurement should be done accordingly.

2. Sizing the appropriate meniscal allograft should be done by radiographs, MRI or CT. At present it is not clear how important sizing of the meniscal allograft is and by which technique sizing is done most accurately.
3. The mechanical axes provide the description of load transmission through the knee joint. When there is varus or valgus malalignment abnormal stress will occur on the medial or lateral tibial plateau, respectively. The rationale for upper tibial osteotomy is to correct the abnormal loading stress on the knee that is caused by the abnormal mechanical axis in the coronal plane. The excessive load on the medial compartment of the joint in varus deformity is transferred, in a more normal amount, to the lateral compartment, with pain relief as clinical result. [128] When meniscal transplantation is indicated in a knee joint with an abnormal mechanical axis, this malalignment is proposed to cause abnormal pressure on the meniscal allograft resulting in impaired revascularization that will lead to degeneration and loosening of the graft. For that reason a normal mechanical axis of the knee joint in the coronal plane is advised in meniscal transplantations.
4. It is known that in knee joints with insufficiency of the ACL the menisci are at secondary risk of damage; *in time the frequency of meniscal tears increases significantly.* [56] The results in meniscal repair studies show that meniscal healing occurs up to 96% in stable knees. [80] And in significantly lower rates in deficiency of the ACL. [129] Since the menisci are secondary stabilisers, they will be at risk in unstable knees. Therefore meniscal allografts should only be transplanted in stable joints, or in conjunction with a reconstruction of the ACL.
5. How to fix the allograft in the knee is still not clear. Different techniques have been described; open or arthroscopic assisted, with or without bone blocks to secure the meniscal horns, and with transosseous sutures and a bone bridge for tying the meniscal horn sutures. [110, 130-133] There is evidence that securing the meniscal horns reduces the contact pressure on the articular cartilage in contrast to meniscal horns that are not secured. [132, 134] Fukubayashi and Kurosawa have shown that there are anatomical and biomechanical differences between the medial and lateral meniscus. [135] Van Arkel and de Boer showed that it is not possible to compare the results of lateral and medial meniscal allografts (**Chapter 6**). Therefore, it could be possible that the best technique to secure the donor meniscus is different for the lateral and medial allograft.
   Although contact pressure on articular cartilage is reduced after securing the allograft horns, there is no evidence in animal and human studies that meniscal

transplantation protects articular cartilage after meniscectomy, even though at arthroscopic evaluation no sign of progressive deterioration was shown. [133, 136-139]

6. There is no general accepted and scientifically proved postoperative rehabilitation protocol after meniscal transplantations, but most authors include a period of non-weight-bearing, combined with continuos passive motion, with restricted range of motion, with or without brace, followed by a period of progressive weight-bearing as tolerated. Cycling and swimming is promoted. From 6 to 12 months return to previous activities is recommended, but contact sports are not advised until 12 months postoperatively. [110, 140-142]

Meniscal transplantation; The Rationale

In the past it was recognized that a torn meniscus gives significant clinical symptoms and could cause secondary damage to the articular cartilage. Smillie warned about the importance of removing the entire meniscus because of the danger of leaving behind unrecognized posterior horn and intrameniscal defects or secondary and possible tertiary bucket handle tears. He also suggested that a bucket handle fragment should be removed only if the meniscus cannot be removed without damaging the joint. In his experience, a meniscus that has regenerated after total meniscectomy in general takes the same form and appearance as the original structure, although it may be somewhat smaller or thinner. [143] The standard treatment was total meniscectomy to provide meniscal regeneration. However, the late results after total meniscectomy showed a high incidence of osteoarthritis of the knee joint. The incidence of osteoarthritis after meniscectomy varies between 50 to 70 % after 10 to 20 years. [2, 5] On review of the radiographs of patients who had a total meniscectomy 10 or more years before, Tapper and Hoover identified in 85% of the cases the site of the meniscetomy correctly. Like Veth, they also noted the discrepancy between the deterioration in radiological appearance and the clinical results after total meniscectomy. [4, 144] After medial meniscectomy 80% had a good or excellent clinical result, whereas this was 50 % after double and 47% after lateral meniscectomy. [4] In a recent study, using the Ahlbäck radiological criteria as signs of osteoarthritis, the incidence of narrowing of articular cartilage was 36% at 30 years of follow-up. [35]

Because of the greater role in stress protection of the lateral meniscus compared to the medial meniscus, lateral meniscectomy will be followed by a higher incidence of osteoarthritis. [5, 32, 33] After 30 years the clinical results of total medial meniscectomy were best, followed by lateral meniscectomy and worst after both medial and lateral meniscectomy of the same knee. [35] McGinty et al. showed that partial meniscectomy gave better subjective functional results, better anatomical

and radiological results, and less postoperative complications. [31] Cox et al resected the medial meniscus in dogs' knees and showed that the degenerative changes after meniscectomy were directly proportional to the amount of tissue removed. [6] It is now generally accepted that if meniscectomy is indicated, arthroscopic partial meniscectomy is the treatment of choice. Meniscectomy is not the only prognostic factor for the development of osteoarthritis. There is also a genetic predisposition. Risk factors for the development of tibiofemoral osteoarthritis like meniscectomy are; obesity, physical activity and previous knee injury, while Heberden's nodes and family history are more closely associated with patellofemoral involvement. [146,147]

Because in time more basic interest in the meniscus arose, arthroscopic surgery developed, and partial meniscectomy and meniscal repair could evolve.

As stated previously the indications for meniscal repair are longitudinal lesions within the vascular part of the meniscus. Contra-indications include stable longitudinal tears shorter than 1 cm, partial thickness tears, degenerative tears and joint instability. The first should be treated non surgically, the others surgically. If meniscal repair is indicated in a knee with instability of the ACL, the repair should be done in conjunction with an ACL-reconstruction. [69] Other factors that influence the results of meniscal repairs are the rim width, tear length and duration of symptoms. [86] Meniscus related surgical treatment decisions between repair or partial meniscectomy are based on location, extent of damage, size, stability of the meniscal tear and the activity level of the patient. Total meniscectomy is reserved for tears for which any other option is not suitable. [145]

(Sub)total meniscectomies are performed, but rarely. In the long term they will lead to compartmental osteoarthritis in relatively young and active people. If the compartmental osteoarthritis becomes disabling and the alignment of the joint is normal, these patients could not be helped with a corrective osteotomy, and they are to young for an arthroplasty. If in these patients the progression of the degenerative changes in the knee joint could be delayed or even stopped, than transplantation of the meniscus could be an alternative therapy. To achieve this the meniscal allograft has to grow to the knee capsule to perform the biomechanical function in the knee, without an immunologically provoked inflammatory response, and pain and disability should improve significantly. To evaluate these improvements the indication should be used very strictly, the preoperative and postoperative assessment protocol should include clinical -, radiological - and arthroscopic criteria and describe histological and laboratory findings.

In **Chapter 2** it is determined whether meniscal transplantation is possible in man, whether the allograft will grow to the knee capsule, and the short-term results are assessed. The correlation between clinical results, MRI and arthroscopy is described in **Chapter 3**. Some preliminary immunological aspects are described

in the following chapters. The study described in **Chapter 4** is performed to determine the presence of antibodies against HLA antigens in recipients of meniscal transplants. In **Chapter 5** we explored the possible occurrence of red cell sensitization after transplantation of meniscal allografts. Finally, in **Chapter 6** a prospective survival analysis of 63 consecutive meniscal allografts transplanted into 57 patients is presented.

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2 Human meniscal transplantation; preliminary results at 2 to 5 year follow-up

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Abstract

In a prospective study, we evaluated the clinical results of 23 patients with a cryopreserved non-tissue-antigen-matched meniscal transplant at a follow-up of from two to five years. These early results were satisfactory in 20 patients. Three transplantations failed and the allografts were removed after 12, 20, and 24 months. Post-transplantation arthroscopy showed that most meniscal transplants had healed to the knee capsule. Histological examination showed revascularisation of the transplant and evidence of viable meniscal chondrocytes. The failures were probably caused by malignment, resulting in impaired revascularisation of the graft.

Introduction

Menisci play an important role in load transmission, joint stability, lubrication and nutrition of articular cartilage.[1-3] Total lateral meniscectomy leads to a higher incidence of osteoarthritis than loss of the medial meniscus, because of the greater role of the lateral meniscus in stress protection. [4-6] The medial meniscus is more important in joint stability. [7]

Clinical, experimental and biomechanical investigations have shown that meniscectomy can lead to degenerative changes in the knee. [1, 4-6, 8-13] Partial meniscectomy has less effect than total meniscectomy. [11,14,15] The results of arthroscopic meniscectomy are better than those seen after the open procedure. The best results are achieved by arthroscopic partial meniscectomy. [16, 17] Because

of these degenerative changes, the technique of meniscal suture was developed to repair the torn meniscus. [18,19] The first results have been encouraging. [20-23]

Total meniscectomy, leading to compartmental osteoarthritis of the knee, produces a clinical problem. When there is malalignment of the knee with overload on the compartment with osteoarthritis, a corrective osteotomy is preferable. If the patient is older than 55 years, a unicondylar or total knee arthroplasty may be considered. For younger patients, reconstruction of the missing meniscus is a possibility. Studies to reconstruct or substitute menisci with a teflon-net, carbon fibre-polyurethane grafts, copolymeric collagen scaffolds, or a dacron prosthesis are still experimental. [24-28] Replacement of the absent meniscus by meniscal transplantation is an alternative method of treatment. The technique has been described in man, sheep, dogs, and goats. [29-34] The indication for meniscal transplantation in this study was a patient under the age of 55 years with a disabling compartmental osteoarthritis after a meniscectomy.

We performed the present preliminary study to determine whether meniscal transplantation is possible in man, whether the allograft meniscus will grow to the knee capsule, and to analyse our short-term results.

Patients and Methods

Between 1989 and 1993 we performed 23 cryopreserved non-tissue-antigen-matched human meniscal transplantations. There were 17 men and 6 women of average age 41 years (30 to 55). The lateral meniscus was transplanted in 14, the medial in seven and both in the same knee in two. The average interval between total meniscectomy and transplantation was 16 years (3 to 33) and the average duration of follow-up was 36 months (24 to 60). Details of the patiens are given in Table 1.

Physical examination before transplantation showed eight patients with a stable knee after meniscectomy, nine with instability due to meniscectomy, and six with instability due to meniscectomy and rupture of the anterior cruciate ligament confirmed by arthroscopy. Knee stability was tested by the Lachman and the anterior-drawer tests.

Preoperative planning. Preoperatively, routine radiographs of the knee were taken. The alignment of the joint was measured by drawing the biomechanical axis on full-lengths weight-bearing radiographs. A diagnostic arthroscopy was performed before transplantation was planned to determine the state of the knee and especially the articular cartilage. Arthroscopic findings were tape on video. The results of the diagnostic arthroscopies are shown in Table 2.

Collection of the graft. The donor menisci were obtained from a tissue bank in the United States. Meniscal allografts were procured to the methods reported by

Malinin et al..[35] Donors met the criteria outlined by the American Association of Tissue Banks. The graft (two menisci and the tibial plateau) was removed under sterile conditions, washed in a 15% glycerol tissue-culture solution, and then frozen to -80^{0}C in two stages. After freezing, the grafts was transferred to a liquid nitrogen freezer for storage. Histocompatibility testing was not performed. Selection of the required size of the allograft was based on radiography.

Preparation and implantation of the allograft. A medial or lateral arthrotomy was used. The medial or lateral gastrocnemius muscle was seperated from the capsule to protect the neurovascular bundle. The capsule was opend anterior to the collateral ligament, leaving a small part attached to the anterior rim of the tibia. In three cases the medial ligament was detached from the femoral condyle to obtain a better exposure. Meanwhile, the allograft was thawed in a 0.9% saline solution.

The lateral or medial meniscus was then prepared from the allograft tibial plateau on a side table. Six to nine non-absorbable sutures, with two long needles, were placed in the middle and posterior part of the donor meniscus. Under direct vision all the needles, with the posterior horn first, were pulled, from inside the knee, through the capsule. Knots were made on the outside of the capsule gradually pulling the meniscus backwards into the joint. With the allograft in place, the anterior part was stitched to the capsule still attached to the anterior rim of the tibia. The anterior horn of the transplanted meniscus was sutured in an anatomical position to the tibial plateau after partial excision of the fatpad and local removal of osteophytes. All operations were performed by the senoir author (HHdB). Cefamandol (1g) was given three times a day, for five days intravenously, and low-molecular-weight heparin (7500 IU) was injected once a day subcutaneously, until the patient began mobilisation. Immunosuppression was not given.

Postoperative management. On the fifth day postoperatively the patient was mobilised non-weight-bearing, with the knee protected in a removable cast. Continous passive motion was started and given four times a day for one hour. When 90^0 of passive flexion had been attained, usually after about ten days, the patient was discharged from hospital non-weight-bearing. The knee was exercised daily, under the guidance of a physiotherapist. Weight-bearing began at six weeks, with full weight-bearing at nine weeks. The patients were encouraged to walk, swim and cycle.

Evaluation of results. A strict protocol was used, including the Knee Assessment Scoring System, the modified Lysholm score, and the Tegner activity scale. The Knee Assessment Scoring System (KASS) was described by Mahomed et al., and includes subjective (60 points) and objective (40 points) data (36). A succesful result requires improvement of the KASS by at least 10 points, or maintenance of a score of 75 points or higher. The Lysholm score is a knee function score with a

Table I. Details of 23 patients who had meniscal transplantation

Case	Sex	Age (yr)	Knee allograft	Interval¶ (yr)	Follow-up (mth)	KASS		Lysholm score		Tegner score			Alignment		Fairbanks		ACL rupture	Instability	
						Preop	Postop	Preop	Postop	Pre-trauma	Preop	Postop	Preop	Postop	Preop	Postop		Preop	Postop
1	M	49	R, Lat	16	60	26	96	6	88	4	0	1	0	Unchanged	1	1 RA†	No	None	None
2	F	30	L, Lat	14	57	39	86	19	85	7	3	3	0	Unchanged	1	1	No	Ant med	None
3	M	40	R, Lat	16	54	29	89	31	92	5	0	3	0	Unchanged	1	1	No	Ant med	None
4	M	36	L, Lat	10	50	39	89	8	88	5	5	4	0	Unchanged	1	2	No	Ant lat	Ant lat
5	M	31	L. Lat	7	46	33	86	5	72	5	0	4	0	Unchanged	2	2	Yes	Ant	Ant
6	M	51	R, Lat	8	46	27	76	15	76	7	0	0	Valgus 3	Unchanged	0	2	No	Ant lat	Ant lat
7*	F	37	R, Med	11	18	32	37	17	19	4	3	2	Varus 4	Varus 6	1	1 RA	Yes	Ant	Ant
8	F	40	R, Lat	21	43	50	85	31	71	9	0	2	Valrus 6	Unchanged	1	1	No	None	None
9	F	46	R, Med	16	42	40	95	28	86	8	1	3	0	Unchanged	3	3	No	None	None
10	M	39	R, Lat	3	41	41	89	17	65	9	0	2	Valgus 3	Unchanged	2	2 RA	No	Ant lat	None
11	M	40	L, Med	20	39	46	84	36	65	9	3	3	0	Unchanged	2	2	Yes	Ant med	None
12*	M	52	L, Med	7	24	26	45	15	55	8	0	3	0	Unchanged	2	2 RA	A+PCL	Ant med	Ant med
13	F	40	L, Lat	11	37	33	97	28	85	7	3	4	0	Unchanged	0	0 RA	No	None	None
14	M	40	R, Lat	20	36	45	89	32	83	9	1	2	0	Unchanged	0	1 RA	No	None	None
15	M	50	BL+M	32	35	43	89	40	92	6	0	3	0	Unchanged	0	2 RA	No	Ant	None
16	M	36	R, Lat	7	31	31	84	18	82	9	4	4	0	Unchanged	1	2	Yes	Ant med	Ant med
17	M	30	L, Med	14	30	41	89	46	86	9	0	5	Varus 2	Unchanged	1	1	No	Ant med	None
18*	M	55	L, Med	33	12	27	45	24	41	9	5	3	Varus 3	Unchanged	0	0 RA	No	Ant med	Ant med
19	M	35	R, Lat	18	28	25	93	25	83	9	4	4	Valgus 3	0	1	1 RA	No	None	None
20	M	32	R, Lat	13	27	31	89	15	86	9	0	7	Valgus 3	0	2	2	No	None	None
21	M	52	L, Med	30	26	28	93	45	92	9	5	2	0	Unchanged	1	1	PCL	None	None
22	F	41	R, Lat	25	24	33	77	46	82	9	1	1	0	Unchanged	1	1 RA	No	Ant lat	None
23	M	31	R, L+M	6	24	36	80	25	75	9	2	3	0	Unchanged	1	1	No	Ant	Ant
Average		41		16	36	35	82	25	76	8	2	3			1	1			

* scores at retrieval of allograft
† retropatellar arthritis
¶ time from meniscectomy to transplantation

maximum of 100 points (excellent >94 points, good 84 to 94, fair 65 to 83, and poor < 65 points). The Tegner activity scale shows the activity level of a patient to a maximum of 10 points. The protocol was scored preoperatively and postoperatively every six months.

Radiological evaluation was performed according to the Fairbanks criteria at six-months intervals postoperatively (Table 1). At the time of follow-up, the mechanical axis and weight-bearing line measured on full-standing radiographs were compared with those preoperatively.

Post-transplantation arthroscopy (PTA) was performed in 12 patients. Seven had one arthroscopy, four had two, and one had three arthroscopies after transplantation, combined with a small needle biopsy of the donor meniscus. In all except one case the first PTA was done for investigation; case 7, however, had no pain relief after eight months.

PTA's were performed at different time intervals, varying from 6 to 40 months. In each case three biopsy specimens were taken from the outer one-third of the transplant, at the anterior horn, the mid portion, and the posterior horn. The material was stained with hematoxylin and eosin, and azan. Enzymic histochemical reactions were also performed. Hydrolytic enzymes (alkaline phosphatase and alpha-naphthylacatate(NA)-esterase) were used to detect degenerative changes in chondrocytes and collagen structure and oxidoreductase enzymes (nicotamide-adenine-dinucleotide (NADH)) were used as markers of mitochondrial activity.

Because the transplants are not expendable, cell proliferation was evaluated only in the allografts which had been removed on the basis of proliferating cell nuclear antigen (PCNA) and Ki-67 counts, as described by Dervan et al and de Boer and Koudstaal. [37-38]

The clinical criteria for failure of a meniscal allograft were persistent pain, an unsuccesful result in the KASS or a poor result in the modified Lysholm score.

Control material. The contralateral menisci of the donor tibial plateau were used as control specimens. These menisci had been treated and cryopreserved like the implanted menisci and were analysed in the same way as the needle-biopsy material.

Results

Clinical evaluation. According to the KASS, 20 patients had a successful and three an unsuccessful result. Evaluation by the modified Lysholm score at time of follow-up showed 10 with a good, 10 with a fair, and 3 with a poor result (Table 1). In the three poor results, meniscal transplantation was unsuccessful because the allograft had become detached from the capsule. The allografts were

removed in cases 7, 12 and 18 after 20, 24 and 12 months respectively. Another patient who had a partially detached posterior horn after 40 months required partial meniscectomy.

Most patients regained almost full function in the first six months after transplantation. The KASS showed an increase from preoperatively 35 to 82 at follow-up in the whole group, the average Lysholm score increased from 26 to 75, and the Tegner score increased from 2 to 3 (Table 1).

Physical examintation at follow-up showed that five of the six patients with instability due to rupture of the anterior cruciate ligament were unchanged. Six patients, with instability due to meniscectomy, showed no instability after transplantation (Table 1).

Arthroscopy after transplantation. Arthroscopy was performed in 12 patients at different intervals. As stated earlier, the first PTA in each patient was done for investigational purposes. In seven patients the transplanted menisci had healed to the knee capsule. The five other patients had partially detached meniscal allografts. Four were stitched back to the capsule and in one, partial meniscectomy was performed. Loosening of the graft in one patient (case 3) was related to a torsional injury in a motor-vehicle accident. A second-look arthroscopy, after reattachment, showed complete healing. Because of the clinical signs of loosening and locking, three medial meniscal allografts had been removed after a second PTA. In two the transplanted meniscus showed good fixation to the knee capsule initially, but they eventually became detached. The third was removed as reattachment was unsuccessful.

Signs of degeneration of the allograft, described as "changes in colour" and "surface irregularities" noted during PTA, were seen in three and four cases, respectively. Colour changes occurred only in the three patients in whom the allografts were removed (cases 7, 12, and 18). The surface irregularities were seen in cases 4, 7, 8, and 18. Degenerative tears had not occurred.

When the pre- and post-transplantation arthroscopies were compared there were no signs of progressive deterioration or improvement of the quality of articular cartilage.

Histological and histochemical evaluation. Biopsy material is difficult to evaluate. First, cellular distribution in meniscal tissue is not uniform, and secondly, the transplant is not expendable. Despite these problems, histolgical analysis showed degenerative changes, classified as changes in cellularity and structural integrity, not seen in the control menisci. These were independent of the time after transplantation. Histochemical reactions (NADH-reductase) shown by the control menisci indicated viable cells at time of transplantation. Biopsy specimens of the allografts six months after transplantation indicated an increase in mitochondrial

Table II. Arthroscopic evaluation

Case	Pretransplantation diagnostic arthroscopy			Post-transplantation arthroscopy (mth)
	Meniscectomy	ACL	Compartment chondrosis	
1	Lat total	Intact	Lat grade 4	6
2	Lat+med total	Intact	Lat grade 3	12 30
3	Lat+med total	Intact	Lat grade 3, med grade 1	8 12* 40
4	Lat total, med part	Intact	Lat grade 3	18
5	Lat+med total	Rupture	Lat grade 3, med grade 2	18*
6	Lat+med total	Intact	Lat grade 3, med grade 2, retropat grade 2	40†
7	Med total	Rupture	Med grade 3, retropat grade 3	8 20
8	Lat total	Intact	Lat grade 3	12 28
9	Lat part, med total	Intact	Lat grade 2, med grade 3	
10	Lat total, med part	Intact	Lat grade 3, retropat grade 2	9
11	Lat total, med total	Rupture	Lat grade 1, med grade 3	
12	Med total	Rupture	Lat grade 1, med grade 3, retropat grade 3	24
13	Lat total	Intact	Lat grade 3, retropat grade 1	
14	Lat total, med part	Intact	Lat grade 3	
15	Lat+med total	Rupture	Lat grade 3, med grade 3, retropat grade 2	9
16	Lat total, med part	Rupture	Lat grade 3	
17	Med total	Intact	Med grade 3	
18	Med total	Intact	Med grade 3	6* 12
19	Lat total	Intact	Lat grade 3	
20	Lat total	Intact	Lat grade 3	
21	Med total	Intact	Med grade 2	
22	Lat total	Intact	Lat grade 3,	
23	Lat part, med total	Intact	Lat grade 3, med grade 3	

* partially detached, stitched back
† partially detached, partial meniscectomy

activity, which had returned to normal. Hydrolytic enzymes (alpha-NA-esterase) were not significantly changed.

Histological analysis of the retrieved allografts showed very few viable cells as well as degenerative changes in chondrocytes and collagen structures. Neither lymphocytes nor histiocytes were found in the meniscal cartilage. In the parts of those menisci which were still attached to the capsule, there was vascular ingrowth with vital cells in the vicinity. [38]

Cell proliferation was evaluated in the three removed meniscal allografts. The indicator KI-67 sporadically showed a synoviocyte with a positive nucleus. Fibrocartilaginous tissue was negative for PCNA and Ki-67. [38]

Immunology. No histological signs of rejection were found. There was no infiltration of lymphocytes or histiocytes into the transplants, including the cases in which the allografts were removed. At PTA six patients had a slight synovitis and joint effusion.

Radiological evaluation. A steady state, according to the Fairbanks criteria, was

found in 18 patients. The other five patients showed an improvement (Table 1). Preoperatively, the radiographs of nine patients had shown signs of retropatellar osteoarthritis. Follow-up radiographs showed no ossification or calcification in the transplanted meniscal tissue.

Eight patients in this series did not have neutral alignment. Their average KASS and Lysholm score were 75 and 65, respectively. The average score of the patients with a neutral alignment was 85 and 81, respectively. Two cases are of special interest. One patient (case 7) had a progressive varus malalignment after 20 months. Clinically, this was considered as a failure. In another (case 8) a varus malalignmnt of 6^0 did not change after transplantation. This patient had undergone two corrective osteotomies previously, because of lateral compartmental osteoarthritis and valgus malalignment.

Complications. No major complication in the form of neurovascular lesions, thrombosis, or wound infections occurred, but five patients developed minor complications due to non-absorbable sutures. They had pain anteriorly. Granulomas developed around the suture knots. These were removed during PTA. Thereafter absorbable sutures were used and no further granulomas developed. At present, the posterior part of the allograft, that is the part of the allograft posterior to the collateral ligament, is fixed with non-absorbable sutures and the part anterior to the collateral ligament with absorbable sutures.

The control menisci. All but one of the control menisci appeared macroscopically, microscopically and histochemically normal. In one patient only (case 2), there were signs of degeneration after cryopreservation. The patient did well clinically. Proliferating markers (PCNA and Ki-67) were absent in the control menisci of the transplants.

Discussion

For the long-term survival of human meniscal allografts there are two prerequisites. The viablity of meniscal chondrocytes must persist after cryopreservation and transplantation and the viable cells must synthesise collagen, which ensures the integrity of the extracellular matrix, so that the meniscal allograft can perform its biomechanical function. Because in adults only the outer one-third is vascularised, the synovial fluid plays an important part in nutrition. [39-41] Our results showed an increase in the KASS and the average Lysholm score. Overall evaluation showed a satisfactory results in 20 patients with three failures.

Free human meniscal transplantation has been described by Milachowski et al., Garrett et al., and Verdonk. [29, 32, 34] Milachowski et al. reported six patients who received deep-frozen meniscal transplants and 16 who had lyophilised menis-

cal transplants. [29] Garret et al. reported six patients, of whom three had no complaints of pain, and three had occasional minimal pain but no locking; follow-up ranged from 24 to 44 months. [32] Although Verdonk used free meniscal transplants, he also performed corrective osteotomies during the same procedure, and his results are therefore not comparable. [34]

Our study showed that at follow-up arthroscopy most meniscal allografts were firmly attached to the knee capsule, although in some cases only after further arthroscopic attachment. Improvement of articular cartilage, as seen by Milachowski et al., was not cofirmed. [29] In some patients the radiological score based on the Fairbanks criteria changed for the better. Nevertheless, the numbers are to small to allow statistical analysis or conclusions as to clinical significance.

For elective meniscal transplantations, methods for the preservation and storage of the tissue have been developed. Jackson et al. reported only 30% viability of cryopreserved meniscal chondrocytes immediately after thawing from 30 days of storage at -80^0C. [33] Arnoczky et al. found that in dogs, although cryopreservation and short-term storage apparently had no influence on the morphological appearance or biomechanical character of the meniscus, only 10% of the meniscal cells were viable, and even these were hypermetabolic. [30] In time this increased metabolic activity returned to normal.

Our histochemical results showed that viability after cryopreservation of the menisci appeared normal and increased metabolism was seen in the first months after transplantation. In due course, the metabolism returned to normal. This could indicate a " repair phase", a phenomenon also observed by Arnoczky et al. [30] The underlying mechanism, however, is still unkown. Theoretically, after cryopreservation, the viable cells could multiply and produce new extracellular matrix. Although in the present study cell proliferation was evaluated only in the three cases of clinical failure, the findings in both the removed allograft material and the control menisci were negative for the proliferation markers PCNA and Ki-67. [38]

A second explanation of the repair phase is that regeneration of the allograft takes place by migration of modified synoviocytes along proliferating vessels. Our study showed that parts of the transplanted menisci had been revascularised and remained vital, as shown by the histochemical results. The mitochondrial activity of the chondrocytes in the revascularised parts was not reduced. This suggests a third explanation, that the meniscal chondrocytes remain metabolically active if revascularisation occures, after a period of hibernation. The Ki-67 antigen and the PCNA are both expressed in all the phases of mitosis except G0 and early G1 (the resting phase of the cell cycle), but not in quiescent cells. [37] The growth potential of the graft as shown by the proliferation markers Ki-67 and PCNA seemed to be practically nil. [38]

The common and important factor in both the second and the third theories is revascularisation of the allograft. Factors causing impairment of this are malalignment and joint instability. Because our findings indicate that patients with a preoperative malalignment had poorer results, we suggest that malalignment causes abnormal pressure on the graft. This could be responsible for impairment of revascularisation or cause vascular damage in a later phase, with degeneration and loosening of the transplant. As stated by Beaver et al., allograft survival depends more upon biomechanical factors than upon graft rejection. [42] Half the patients with an intact anterior cruciate ligament showed no preoperative instability. The other half showed improvement of joint stability after meniscal transplantation. This can be explained by better congruity between the femoral condyle and the tibial plateau. In those with a ruptured anterior cruciate ligament no improvement of joint stability was noted.

Another important factor in transplant surgery is immunogenicity. Intact articular cartilage is thought to be immunogenetically priviliged, because the matrix prevents exposure of chondrocytes. [43] No signs of inflammation or rejection were observed in our study. The problem for histological analysis is that cell distribution is not uniform in meniscal tissue and the transplants are not expendable; this has not been solved. Future studies using electron microscopy may be of help.

Conclusion

Short-term results of this preliminary study show that meniscal chondrocytes can survive cryopreservation and transplantation. Technically, the meniscus can be transplanted in man. The allograft attaches firmly to the knee capsule, and is followed by revascularisation of the graft. Revascularisation is necessary for the vitality of meniscal chondrocytes in the resting phase, that is to start mitosis and synthesis of extracellular matrix. Although meniscal transplantation is still experimental, it can be an alternative method of treatment for postmeniscectomy osteoarthritis. The results of meniscal transplantation are better in patients with normal alignment of the knee. Therefore malalignment should be corrected before or at the time of meniscal transplantation. Further studies and longer follow-up are necessary to show whether meniscal transplantation will prove durable and prevent progressive degeneration of articular cartilage in the long-term.

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3 Meniscal allografts: evaluation with magnetic resonance imaging and correlation with arthroscopy

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Abstract

Purpose: To correlate clinical results to magnetic resonance imaging (MRI) and arthroscopy after cryopreserved non-tissue-antigen matched meniscal transplantations. *Type of Study:* Blinded; the observers were blinded for each others' assessment. *Materials and Methods:* Sixteen consecutive patients were included in the protocol. First, clinical evaluation and MRI were performed. Second, within 24 hours, arthroscopy was performed. *Results:* The clinical results showed better correlation between clinical results and arthroscopy than between clinical results and MRI. In the present study, MRI was not benificial in evaluating meniscal transplants. *Conclusions:* Using more sophisticated MRI techniques, the correlation between clinical results, arthroscopy, and MRI could probably be improved.

Introduction

Human meniscal transplantation is an experimental treatment for postmeniscectomy osteoarthritis of the knee joint. In selected patients, short-term results are promising. The indication for meniscal transplantation in this study was a disabling compartmental osteoarthritis resulting from previous total meniscectomy and a normal alignment of the knee joint. To evaluate the results, a clinical scoring system and radiological criteria were used. For investigational purposes, post-transplantation arthroscopy was performed.

Arthroscopy is an invasive procedure, whereas magnetic resonance imaging (MRI) is noninvasive and is accepted as a diagnostic tool in the detection of

meniscal pathology. The role of MRI in assessing meniscal healing is less clear. Furthermore, MRI would be beneficial if it had either positive or negative correlation with the clinical results. The purpose of this study was to correlate the clinical results to MRI findings and to evaluate whether MRI predicts arthroscopic outcomes after meniscal transplantation.

Patients and Methods

The indication for meniscal transplantation was patients younger than 55 years of age with a disabling compartmental osteoarthritis after a meniscectomy. Diagnostic arthroscopy was performed before transplantation to determine the state of the knee.

Between October 1994 and November 1995, 16 consecutive patients were scheduled for arthroscopy after cryopreserved non-tissue-antigen matched meniscal transplantation. Voluntary participation and informed consent was obtained in all cases. First, a strict protocol was used for clinical and radiological evaluation, including the Knee Assessment Scoring System (KASS), the modified Lysholm score, and the Tegner activity scale.[1] Second, arthroscopy was performed within 24 hours. Before arthroscopy, the knee joint was tested under anesthesia. The radiologists (R.G.,I.d.P.), and the arthroscopist (E.v.A.) were not informed of the results from the other departments.

The clinical criteria for failure of a meniscal allograft were persistent pain, an unsuccessful result in the KASS, or a poor result in the modified Lysholm score. According to the KASS, a successful result requires improvement by at least 10 points, or maintenance of a score of 75 points or higher. The Lysholm score defines excellent as >94 points, good 84 to 94, fair 65 to 83, and poor <65 points. MRI criteria for success was a meniscal allograft completely healed to the capsule; unsuccessful results were defined as a totally or partially detached meniscal allograft or an allograft with a grade 3 intrameniscal signal. A totally or partially detached allograft or a meniscal tear diagnosed at arthroscopy was considered an arthroscopic failure. An allograft totally healed to the capsule with no meniscal tear was considered an arthroscopic success.

The MRI results were interpreted by 2 radiologists (R.G.,I.d.P.), and a preaccepted scoring list was filled in on the basis of consensus. The classification of meniscal lesions was based on the scoring system of Creus and Stoller.[2] The second-look arthroscopy was videotaped and compared with the videotape of the arthroscopy before meniscal transplantation. The arthroscopic findings and surgical procedures were documented in a standard report.[1] Detachment and meniscal tears were classified according to Cooper et al.[3]

MRI Technique. The MRI studies were performed on a 0.5-Tesla magnet. Sagittal and coronal imaging were performed with a 16- x 13.5-cm wrap-around extremity coil. Sagittal and coronal plane images were obtained in 3-mm sections with an interslice gap of 1.5 mm. All T1, T2, and STIR sequences provided 20 images. The T1-weighted images were generated with a TR of 475 ms, a TE of 25 ms, a 256 scan matrix, a 256 reconstruction matrix, and 1 NEX. The T2-weighted images were applied with the turbo spin-echo technique with a TR of 3,500 ms, a TE of 80 ms, a flip angle of 90^0 , a scan matrix of 256, and a recontruction matrix of 256. For STIR, we used a TR of 1,500 ms and a TE of 30 ms.

Mensical tears were classified on MRI according to Creus and Stoller.[2] Grade 1 MR signal intensity is defined as globular and is not adjecent to either the superior or inferior articular meniscal surfaces. Grade 2 MR signal is primarily a linear signal within a meniscus that does not extend to an articular surface, and a grade 3 intrameniscal signal reaches at least 1 meniscal articular margin.

Extrusion of the allograft was defined as the portion of the allograft that was displaced completely over the peripheral border of the tibial plateau. Subextrusion meant that the allograft was partially over the border.

Arthroscopic evaluation. At arthroscopy, the healing of the meniscal transplant to the joint capsule was inspected and tested with a probe. The position of the allograft, morphological changes, tears, joint effusion, and synovitis were noted. Articular cartilage morphology was graded according to the Outerbridge criteria.[4]

Stastitical Analysis. Sensitivity, specificity, positive-predictive value, and negative predictive value were calculated from the clinical results, MRI, and arthroscopy. In addition, the likelihood ratio was calculated. The likelihood ratio is an alternative way of describing the performance of a diagnostic test and presents the probability of obtaining a positive test result in a patient with a successful allograft, divided by the probability of obtaining a positive result in a patient with a failed allograft. A likelihood ratio of 1 means that the test adds nothing new to the results. If a likelihood ratio for a positive result reaches infinity or a likelihood ratio for a negative result becomes zero, than the test is more informative.[5]

Results

Clinical evaluation. Between October 1994 and November 1995, 16 consecutive patients were included in the study. There were 13 men and 3 women with an average age of 40 years (30 to 54). The medial meniscus was transplanted in 3 patients, the lateral in 10, and both in the same knee in 3 patients. The average interval between total meniscectomy and transplantation was 16 years (6 to 32). The average duration of follow-up was 32 months (14 to 55).

According to the KASS, 16 allografts (14 patients) had a successful result

TABLE 1. *Details of 16 Patients Who Had Meniscal Transplantation, MRI, and Arthroscopy*

Case	Sex, Age (yr)	Knee, Allograft	Follow-up (mo)	KASS Preop/ Follow-up	Lysholm Scores Preop/ Follow-up	Tegner Scores Pretrauma/ Preop/ Follow-up	ACL Rupture	Instability Preop/ Follow-up	Healing to Capsule		Surgery	Position of Allograft	
									MRI	Arthroscopy		MRI	Arthroscopy
8	F 40	R Lat	55	50 84	31 75	9 0 2	No	None None	Complete	Complete	No	Sub ex	Normal
11	M 40	L Med	49	46 57	36 32	9 3 2	Yes	Ant med Ant med	P/ C, O*	T/ABC, O	Resect	Bucket-hand	Bucket-hand
13	F 40	L Lat	55	33 81	28 90	7 3 3	No	None None	T/ DEF, O†	P/F, O	Part resect	Bucket-hand	Part bucket-hand
15	M 50	R Lat	30	43 83	40 76	6 0 3	No	Ant None	Complete	Complete	No	Ex	Ex
		Med							Complete	Complete	No	Sub ex	Sub ex
16	M 36	R Lat	40	31 84	18 79	9 4 5	Yes	Ant med Ant med	P/ DE, O	Complete	No	Ex	Normal
17	M 30	L Med	36	41 92	46 90	9 0 3	No	Ant med None	T/ ABC, O	P/B, O	Suturing	Sub ex	Sub ex
20	M 32	R Lat	41	31 85	15 86	9 0 2	No	None None	C/ Gr3/ F, 12‡	Complete	No	Ex	Sub ex
23	M 31	R Lat	38	36 59	25 49	9 2 0	No	Ant Ant	Complete	Complete	No	Ex	Sub ex
		Med							Complete	Complete	No	Sub ex	Sub ex
24	M 50	R Lat	26	31 76	15 74	9 0 1	No	Ant None	Complete	Complete	No	Sub ex	Sub ex
		Med							Complete	Complete	No	Ex	Ex
25	M 45	R Lat	25	31 93	19 83	8 4 2	No	None None	P/ D, O	Complete	No	Sub ex	Normal
26	M 32	R Lat	24	36 81	19 74	7 0 0	No	None None	Complete	Complete	No	Sub ex	Sub ex
27	M 36	R Lat	24	33 85	28 85	3 0 3	No	None None	Complete	Complete	No	Sub ex	Sub ex
28	M 40	R Lat	24	53 100	43 92	9 3 5	No	None None	Complete	P/E, O	Suturing	Sub ex	Normal
29	F 43	L Med	18	31 88	41 87	6 0 3	No	None None	P/ A, O	Complete	No	Sub ex	Sub ex
30	M 54	R Lat	16	53 88	39 81	10 3 4	No	None None	Complete	Complete	No	Ex	Sub ex
31	M 36	R Lat	14	51 100	42 95	9 4 6	No	Post Post	P/ BC, O	Complete	No	Sub ex	Sub ex
Average	40		32	39 84	30 78	8 2 3							

Abbreviations: Lat, lateral; Med, medial; Ant, anterior; Post, posterior; Resect, resection; Sub ex, subextrusion; ex, extrusion.
*P/ = partially detached/Cooper classification.
†T/ = totally detached/Cooper classification.
‡C/Gr/ = complete healing to capsule/intrameniscal signal intensity/Cooper classification.

and 3 allografts (2 patients) had an unsuccessful result. Evaluation by the modified Lysholm score showed 1 allograft (1 patient) with an excellent result, 6 allografts (6 patients) with a good, 9 allografts (7 patients) with a fair, and 3 allografts (2 patients) with a poor result. The average Tegner score increased from 1 (0 to 4) to 3 (0 to 5). By definition, 3 allografts (2 patients) were considered as clinical failures. One patient had a complete detachment of a medial meniscal allograft due to anterior cruciate insufficiency. The second patient had persistent pain after a lateral and medial meniscal allograft in the same knee.

MRI evaluation. Twelve allografts had completely healed to the capsule, 5 were partially detached, and 2 were totally detached. In 1 case, the meniscal allograft had completely healed to the capsule but showed a grade 3 intrameniscal signal. Using MRI criteria, 11 allografts were considered successful and 8 were classified as failures.

On MRI, 4 cases were described as having severe shrinkage, and 4 other allografts were described as showing moderate shrinkage. In none of the cases was a normal position of the allograft noted on MRI. Two detached allografts showed a bucket-handle-like configuration, 11 allografts showed subextrusion, and 6 showed extrusion, most frequently of the anterior and middle part of the allograft.

Arthroscopic evaluation. In 11 patients, the post-transplantation arthroscopy was performed for investigational purposes, because of symptoms of locking in 4 patients, and persistent pain in 1 patient. Fifteen allografts had completely healed to the capsule, 3 were partially detached, and 1 was totally detached. The classification according to Cooper et al.[3] is shown in Table 1. In the 3 partially detached allografts, the posterior horn had not healed in 1 case. In the other 2 partially detached allografts, there was no healing in the middle part of the transplant over a length of 1 to 1.5 cm. Both allografts were not luxable while testing with a probe. Refixation was accomplished using an inside-out technique and absorbable sutures. At arthroscopy, no intrameniscal tears were noted in the allografts.

Concerning gross pathology, arthroscopy showed normal meniscal allografts in 15 cases, although the thin free edge was frequently less sharp compared with a normal meniscus. In 4 allografts, a moderate shrinkage of the anterior part was noted. Regarding the position of the allograft, arthroscopy showed 4 allografts with a normal position and 2 that were detached from the capsule and were dislocated mimicking a bucket-handle lesion; 11 showed subextrusion and 2 showed extrusion of the anterior and middle parts.

When pretransplantation and post-transplantation arthroscopies were compared, no differences in the quality of articular cartilage could be seen. Comparing articular cartilage using the Outerbridge grading system, no sign of progressive deterioration was shown, nor was there an improvement in the quality after menis-

Table 2. *Correlation of Clinical Results and MRI*

	Clinical Results		
MRI	Success	Failure	N = 19
Success	9	2	11
Failure	7	1	8
	16	3	

Table 3. *Correlation of Clinical Results and Arthroscopy*

	Clinical Results		
Arthroscopy	Success	Failure	N = 19
Success	13	2	15
Failure	3	1	4
	16	3	

Table 4. *Correlation of Arthroscopy and MRI for Healing to Capsule*

	MRI		
Arthroscopy	Completely Healed	Partially Detached	Totally Detached
Completely healed	11	4	0
Partially detached	1	0	2
Totally detached	0	1	0

cal transplantation. Eight patients had an Outerbridge grade 3, 6 patients a grade 3 to 4, and 2 patients a grade 4 compartment chondrosis.

Cross-correlation. When MRI was compared with clinical results, 9 allografts were successful and 1 was a failure in both (Table 2). Sensitivity was 56% and specificity was 33%; positive-predictive value was 82% and the negative-predictive value was 13%. The likelihood ratio for a positive test result for MRI was 0.84 and the likelihood ratio for a negative test result was 1.3.

When the arthroscopic results were compared with the clinical results, a success in both modalities was noted in 13 allografts and 1 was unsuccessful (Table 3). Sensitivity was 81% and specificity was 33%; the positive-predictive value was

87% and the negative-predictive value was 25%. The likelihood ratio for a positive test result for arthroscopy was 1.2 and the likelihood ratio for a negative test result 0.56.

Correlation of arthroscopy to MRI showed complete healing in both modalities in 11 allografts (Table 4). Four partially detached allografts on MRI showed complete healing at arthroscopy. One completely healed allograft on MRI was shown to be partially detached at arthroscopy. One allograft was shown to be partially detached on MRI, but at arthroscopy it was found to be totally detached. Two totally detached allografts on MRI were seen to be partially detachted at arthroscopy

Discussion

MRI has an established role in the diagnosis of meniscal pathology. The role of MRI in the postoperative evaluation of meniscal healing is less clear. MRI can only be benificial in the postoperative evaluation of meniscal allografts if there is a positive correlation between the clinical results and MRI, and if it can predict the arthroscopic outcome. The results of the present study show that the arthroscopic results correlated better to the clinical results than did MRI. Sensitivity and positive- and negative-predictive value were better for arthroscopy than for MRI. The likelihood ratio for a positive test result for arthroscopy was greater than for MRI. The likelihood ratio for a negative test result was smaller for arthroscopy than for MRI. This means that arthroscopy is a more valid test than MRI in evaluating meniscal allografts. Also, MRI could not predict the arthroscopic results (Table 4). The poor correlation is probably attributable to the MRI technique. A relative low field strength MRI system was used and the intraslice gap of 1.5 mm may account for the overall poor signal-to-noise ratio. At present, a spin-echo proton density (long TR/short TE) or turbo spin-echo (longTR/short TE) is recommended for evaluation of the native meniscus.[6] In their study with a 12-years follow-up after open meniscal repair, Muellner et al. found that, although MRI is an ideal diagnostic tool in discovering meniscal tears, its use in observing meniscal tear healing is limited.[7] Bronstein et al. showed that, within healed meniscal repairs, standard MRI techniques are unable to distinguish scar tissue from meniscal tears. [8] Others recommend MR arthrography for evaluating previously repaired menisci. [9] In contrast, van Trommel et al. showed that noncontrast MRI sequences were more effective in evaluating the physiological state of the repaired meniscus, without artifactual distention of the joint recesses by contrast and air. [10] By using this MRI technique on meniscal allografts, a better correlation could probably be achieved.

To our knowledge, only 3 studies have described MRI after meniscal allografts. [11-13] Patten and Rolffe reported on 3 patients who underwent MRI

between 2 and 14 months after meniscal transplantation. [11] Although preliminary, they concluded that these cases prove that MRI can readily show the morphology and position of the transplanted meniscus. Potter et al. transplanted 29 menisci in 24 patients who underwent MRI an average of 12 months postoperatively, of whom 19 had a second-look arthroscopy. [12] In 16 patients, the time interval MRI and second-look arthroscopy was less than 24 hours, as in our protocol. They concluded that, with appropriate pulse sequences, MRI proved an effective tool in assessing the transplanted meniscus, but they did not provide any statistical analysis. The third study by Verdonk et al. reported on 34 patients with 39 allografts who underwent 103 MRI examinations with follow-up of 2 to 73 months; 12 patients also underwent second-look arthroscopy. [13] They concluded that the correlation between MRI and arthroscopic findings was excellent, but the correlation with clinical outcome was poor; however, no details of the MRI technique or statistical analysis were provided.

Although the general conclusion of these 3 studies was that MRI is useful in the postoperative monitoring of meniscal allografts, the studies had limitations. All were descriptive without statistical analysis and the observers were not blinded to the results. Although limited by the MRI technique, in the present study the observers were blinded for clinical outcomes, MRI success and arthroscopic success were defined independently and were statistically analyzed.

A second aspect in evaluating meniscal transplants is the quality of articular cartilage. Using the Outerbridge criteria during arthroscopy, it is difficult to judge articular cartilage in time. Potter et al. suggested in their MRI study that there exists a correlation between the quality of articular cartilage and the clinical outcome of meniscal transplantations.[12] They stated that patients with moderate to severe chondral degeneration may be at an increased risk of meniscal allograft degeneration, fragmentation, and extrusion, leading to an unfavorable clinical outcome. This statement should be taken with caution because no preoperative MRI studies were performed, and only 8 of 24 patients underwent imaging within 12 hours after meniscal transplantation. In our previous study, we did not find a casual relationship between failure of the mensical allograft and the quality of the articular cartilage. [1] The clinical outcomes of meniscal transplantation are more dependent on biomechanical factors such as joint stability, alignment, and technique to fix the allograft, and immunogenetic properties. [1,14-16] Today, new MRI techniques requiring a 1.5-Tesla MRI scanner have been developed to allow more sensitive imaging of articular cartilage.[17-19] To evaluate this aspect adequately, a study should be designed combining the previously mentioned sophisticated preoperative and postoperative MRI techniques, correlated to clinical results and preoperative and postoperative Outerbridge criteria.

Conclusion

The present study shows that arthroscopy and clinical results correlate better than MRI to clinical results. With highly sophisticated MRI techniques, a more significant correlation could probably have been achieved. The present study also provides definitions for evaluating meniscal transplants.

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4 Human leukocyte antigen sensitization after cryopreserved human meniscal transplantations

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Abstract

The presence of antibodies against human leukocyte antigens (HLA) in recipients of cryopreserved, non-tissue-antigen-matched human meniscal allografts was evaluated. Serological HLA typing was performed for both class 1 and class 2 antigens. The results showed that 11 of 18 recipients became sensitized.

Introduction

Human meniscal transplantation is a new technique in the treatment of patients with osteoarthritis of the knee joint. Although several clinical studies report encouraging results with meniscal transplantation, the indications for transplantation are still not established.[1,2] At present, the patient should be between 20 and 50 years of age and have pain and a disabling compartmental osteoarthritis due to total meniscectomy. The alignment of the limb should be neutral and the knee joint should be stable. The transplantations are described as arthroscopic and as an open procedure, using fresh, cryopreserved, or frozen meniscal allografts. Of special interest is the method of fixation of the transplant. Some authors use allografts with bone blocks for a more stable fixation. Others suture the transplant to the capsule.

Recently, a generalized expression of class 1 and class 2 human leukocyte antigens (HLA) was found in the endothelial and synovial cells of fresh and frozen human meniscal tissue.[3] Because of this generalized expression of HLA antigens, whether meniscal allografts are able to sensitize the host and elicit an immune

response is of interest. The present study was performed to determine the presence of antibodies against HLA antigens in recipients of meniscal transplants.

Patients and Methods

The indication for a cryopreserved, non-tissue-antigen-matched human meniscal transplantation in this series was a patient with a disabling compartmental osteoarthitis of the knee joint caused by total meniscectomy. Procurement, preservation, and transplantation techniques were recently described. [2] The allografts were stitched to the knee capsule, and no bone blocks were used.

Exclusion criteria for this study were a previous transplantation, prior blood transfusion, and previous pregnancies.

Blood samples from the transplant recipients were obtained by venipuncture to determine the HLA antigens and antibodies directed against these antigens. Serological HLA typing was perfomed by standard microcytotoxicity assays for both class 1 and class 2 antigens. Class 1 typing was carried out for 21 A-locus, 50 B-locus, and 10 C-locus antigens. Class 2 typing detected DR1-18, DR5-53, and DQ1-DQ9. Screening for the presence of anti-HLA class 1 and 2 antibodies was performed with a select panel of 64 lymphocytes.

A control group comprised healthy male volunteers with no history of prior transplantation or blood transfusion.

Results

The first 26 consecutive patients (20 males and 6 females) who received a meniscal allograft were ask to participate voluntarily. All except one male answered in the affirmative. Another male was excluded because of a prior perichondrium transplantation. The six females were also excluded because of a history of pregnancies and / or blood transfusion. Thus, 18 patients were included in this study. Classification of the HLA antibodies showed that four patients had both class 1 and class 2 antigens, four patients had class 1 antigens but no class 2 antigens, three had class 2 antigens but no class 1 antigens, and seven had no class 1 or class 2 antigens. The average incubation time, i.e., the interval between transplantation and determination of HLA antigens, was 20 months (5-46).

The preliminary results at 2 -to 5 years follow-up in human meniscal transplantion were recently presented. [2] Post-transplantation arthroscopy was performed in 12 patients at different time intervals for investigational purposes. The results showed healing of the transplanted meniscus to the knee capsule, although some patients required refixation of a partially detached meniscal allograft. Evaluation of biopsy material showed no histological signs of rejection. [2]

One patient (patient 12) who was considered to be a failure after 24

months showed no class 1 or class 2 anti-HLA antibodies at time of allograft removal. The control group consisted of 18 healthy males with no prior transfusion or transplantation. All were negative for class 1 and class 2 anti-HLA antibodies. Donor HLA types were retrieved from the Tissue Bank. The menisci were procured from 18 donors, of whom 4 became multiorgan donors. In the four multiorgan donors, HLA typing was performed. Only one of the recipients (patient 1) showed class 1 antigens (anti-B57). The other recipients were negative for class 1 and class 2 antigens.

Discussion

The short-term results of the meniscal transplantations showed that meniscal chondrocytes can survive cryopreservation and transplantation. [2] The long-term results will depend on immunogenicity and biomechanical factors.

In organ transplantation, anti-HLA antibodies are frequently formed, and correlated with rejection. [4] As in organ transplantation, the outcome of bone allografts is governed by the rules of transplantation immunology. [5] However, intact articular cartilage is thought to be immunogenetically privileged. It does not contain a load of marrow-derived cells, and the matrix prevents exposure of chondrocytes. [5] Little is known about the immune response after mensical transplantation. Articular and meniscal cartilage have a different structure of the extracellular matrix. Therefore, the immune response could also be different. Articular cartilage has a hyaline cartilaginous structure, whereas the meniscus has a fibrocartilaginous structure. In adults, the outer one third of the meniscus is vascularized. Articular cartilage is not vascularized and is completely dependent on the synovial fluid for nutrition.

Recently, generalized expression of class 1 and class 2 HLA antigens was found in cells of the human mensicus. Class 1 antigens were found on fibrochondrocytes, synovial cells, and endothelial cells, whereas class 2 antigens were only expressed on synovial and endothelial cells. [3] Theoretically, meniscal allografts could evoke an immune response and sensitize the host.

A reduction of immunogenicity can be achieved by freezing. Fresh bone allografts are potent immunogens. Frozen grafts are less immunogenic, and freeze-dried allografts produce a relative weak and only infrequently detectable immune response. [6] Freezing human meniscal tissue only slightly reduces the immunogenicity, probably by killing cells and thus decreasing the number of immunologically active cells. [3]

The disadvantage of frozen grafts in meniscal transplantation is cell death, which leads to disintegration of the extracellular cartilage matrix and subsequent loss of biomechanical function. Cell viability can be maintained by cryopreserva-

tion. In a study comparing the antigenicity of fresh and cryopreserved rat valve allografts, it was shown that cryopreservation could not alter the antigenic property of aortic valve allografts. [7]

Another fibrocartilaginous structure is the cornea. The extracellular matrix is more comparable to meniscal cartilage than to articular cartilage. In contrast to the meniscus, the cornea has no nutrient vascular bed.

Experiments with corneal grafts have shown that immune privilege results from (1) the absence of class 2-bearing dendritic cells and macrophages from corneal tissues; (2) the phenomenon of "anterior-chamber-associated immune deviation"; (3) and the immunosuppressive properties of the aqueous humor of the anterior chamber of the eye. [8] These mechanisms could also play a role in meniscal transplantations. Khoury et al. showed that, as in the cornea, fibrochondrocytes in the meniscus are class 2 negative. Histological evaluation revealed no macrophages in the meniscal transplant. [2] An immunology barrier, as in the anterior chamber of the eye, is absent in the knee joint.

Transplanted corneal tissue has proved to be less vulnerable to immune rejection than other types of solid tissue, although high-risk recipients of a corneal graft have an estimated 5-years failure-free graft survival rate of approximately 50%, which is worse than the survival rates for recipients of kidney, heart, or liver transplants. [9] High-risk recipients are those with a previously failed corneal graft, a vascularized corneal recipient bed, or multiple blood transfusions. Collaborative corneal transplantation studies have shown that for high-risk patients who are immunosuppressed by topical steroid therapy, matching and immunosuppression have little to no effect on the survival rate of corneal grafts. [10]

In the present study, there were no high-risk recipients,i.e., no patients with a second meniscal transplantation or prior blood transfusions. Non-tissue-antigen-matched, cryopreserved mensical allografts were used without immunosuppression.

The cellular and humoral immune responses to fresh meniscal allografts were studied in mice. Fresh meniscal allografts in mice did not evoke a remarkable systemic cellular immune response, although minimal lymphocyte invasion into the allogeneic meniscus was observed. [11] These results are consistent with the findings in humans after meniscal transplantation. [1,2] The present study, using non-tissue-antigen-matched, cryopreserved meniscal allografts without immunosuppression, showed antibodies against HLA antigens in 11 of 18 patients, however, without clinical and histological signs of rejection.

The short-term results of meniscal transplantations showed that meniscal chondrocytes can survive cryopreservation and transplantation and that revascularization of the graft will occur. [2] The long-term survival of meniscal allografts may

depend more on biomechanical factors than on immunological factors. In one case, the meniscal transplant failed after 24 months. At the time of graft removal, no class 1and class 2 antibodies were found. The failure was caused by biomechanical factors. The patient had joint instability due to the absence of the anterior cruciate ligament. Now we reconstruct an absent or insufficient anterior cruciate ligament at the time of the meniscal transplantation.

Menisci can be transplanted using two techniques. The allograft can be stitched to the knee capsule in the anatomical position or bone plugs can be attached to the meniscal horn ligament for better anterior-posterior stabilization.[2,12] From an immunological point of view, we would not advocate the use of bone plugs to fix the meniscal allograft because bone plugs contain marrow-derived cells, which increase the antigenic load of the grafts. Biomechanical studies must determinate which is the best technique to fix the meniscal allograft.

Conclusion

The present study shows that recipients of cryopreserved, non-tissue-antigen-matched meniscal transplants can become sensitized. Longer follow-up will reveal the immunological implications of this finding, and more specific analyses will reveal the anti-HLA reactivity in more detail.

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5 No irregular erythrocyte antibodies observed after human meniscal transplants in 32 patients

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Abstract

The presence of irregular erythrocyte antibodies (IEA) in recipients of cryopreserved non-tissue-antigen-matched meniscal allografts was evaluated in 32 patients, prospectively. Blood samples of the recipients were tested pre-operatively and at follow-up. No new IEA's were detected postoperatively, including 6 Rhesus-D negative patients who received a Rhesus-D positive meniscal allograft.

Introduction

Human meniscal transplantation is a new technique in the treatment of patients with osteoarthritis of the knee joint. Human leucocyte antigens (HLA) and blood group antigens were found in human meniscal tissue even after it had been trimmed, frozen and made ready for transplantation. [12] The presence of antibodies against HLA in recipients of cryopreserved, non-tissue-antigen-matched human meniscal allografts were evaluated. The results showed that 11 out of 18 recipients became sensitized. [21] Although cartilage is thought to be immunogenetically privileged tissue to transplant, immunological effects are noted. In bone allografts viable bone marrow cells and bone cells are highly immunogenic. Antigens responsible are cell-surface glycoprotein molecules encoded in the major histocompatibility complex. [8] A reduction of immunogenicity can be achieved by freezing. [5] Nevertheless in several cases the production of red cell antibodies in Rhesus-D negative recipients receiving Rhesus-D positive bone allografts, have been described. [2, 3, 7, 10, 11, 13, 14, 17, 18] On the other hand, in a series of 144 patients, including 30 Rhesus-D-negative patients who received Rhesus-D positive bone, no IEA's were observed. [19] Thus the results in bone allografts so far are inconclusive.

Because of the HLA-sensitization after meniscal transplantation, we were interested in the possible occurrence of red cell sensitization in human meniscal transplantation.

Patients and Methods

32 patients were investigated prospectively. They were tested pre-operatively and at follow-up. 18 patients received a lateral allograft, 11 patients received a medial and 3 patients received both lateral and medial in the same knee. Blood samples were obtained by venipuncture. The donor menisci were obtained from a Tissue Bank in the United States. Donors met the criteria outlined by the American Association of Tissue Banks. The graft was removed under sterile conditions, washed in a 15% glycerol tissue-culture solution, and then frozen to -80 C. After freezing, the graft was transferred to a liquid nitrogen freezer for storage. Implantation of the allograft was done after thawing in a 0.9 % saline solution. The allografts were stitched to the knee capsule, no bone plugs were used to fix the meniscus. None of the recipients received immunosuppression.

All sera were tested for indirect erythrocyte antibodies by the column gel technique of DiaMed (DiaMed ID-Micro Typing system of DiaMed Corporation, Cressier sur Morat, Switserland) using a 3-cell screening panel (DiaMed) with the following blood group antigens C, c, D, E, e, Fya, Fyb, Jka, JKb, K, k, KPb, Jsb, P1, Lea, Leb, Lua, Lub, M, N, S, s, Xga.

Results

Preoperatively 1 recipient had IEA (K fenotype negative). The average lag phase, the time interval between transplantation and determination of IEA's, was 30 months (4-93). Postoperatively, no new IEA's were detected. The 31 recipients did not have IEA's pre- and postoperatively. Seven recipients were Rhesus-D negative, of whom 6 received a Rhesus-D postitive meniscal allograft. Donor ABO blood group and Rhesus factor could not be obtained in 2 cases. The distribution of donor and recipient Rhesus factor is shown in Table 1.

Table 1. The distribution of donor and recipient Rhesus factor.

Recipient	Donor	N = 30
+	+	16
+	–	7
–	+	6
–	–	1

Discussion

We were interested in the possible occurrence of red blood cell sensitization after cryopreserved non-tissue-antigen matched human meniscal allografts.

In blood transfusion it is generally excepted that patients should receive ABO- and Rhesus-D identical blood whenever possible. In contrast to the ABO system, there are no isoagglutinins or naturally occuring forms of anti-D. Rhesus-D negative individuals produce an anti-D following exposure Rhesus-D positive red cells. Rhesus positive patients can receive either Rhesus positive or Rhesus negative blood. Rhesus negative patients should receive Rhesus negative blood. [15] When Rhesus negative recipients are transfused only once with Rhesus positive blood, they have about a 50% chance of forming anti-Rhesus-D-antibodies. [6] It has been reported, that frozen unprocessed human bone allografts contain sufficient red blood cells and red blood cell-antigens to stimulate the production of Rhesus and other red blood cell antibodies in recipients. [2, 3, 7, 10, 11, 13, 14, 17, 18] In one case a nulliparous woman who had never received a transfusion had a bone graft 13 years before her first pregnancy and delivered an infant with hemolytic disease of the newborn due to anti-D antibodies. [7] Like our meniscal allografts, the bone allografts were unprocessed and preserved at -80 C.

The induction of red blood cell antibodies is not uniform. After unprocessed bone allografting in Rhesus-D negative recipients, Stassen et al found no IEA's after bone allografting in 144 recipients, including 30 recipients who were Rhesus-D negative and who received Rhesus-D positive bone. [19] The results in the present study are in accordance with the study by Stassen et al. [19] When bone allografts are processed the red blood cells and the bone marrow are removed. There are no reports of IEA's being induced by the use of processed freeze-dried bone allografts. Therefore when bone allografts are processed matching of the Rhesus type of donors and recipients is not necessary. [4] Disadvantage of freeze-dried meniscal allografts is that they will not survive transplantation as Milachowski et al have shown, whereas cryopreserved or fresh meniscal allografts survive transplantation and are capable to preform the biomechanical function of the meniscus. [16, 22, 23]

The amount of fresh red blood cells that is needed to elicit alloantibody formation to the antigens in the Rhesus-D system is estimated as little as 0.012 to 0.5 ml. [9] The vascularization of the meniscus is only restricted to the outer one-third. [1] Referring to the results of the present study, the amount of red blood cells in the meniscal allograft is probably to small to elicit anti-Rhesus-D-antibodies. When bone plugs are used to fix the menscal allograft, the antigenitic load will be increased.

Conclusion

Although it concerned a small series, the present study showed that no new IEA's were detected. Nevertheless, when unprocessed bone plugs are used to fix the meniscus, we would recommend to give women of the childbearing age who are Rhesus-D negative only Rhesus-D negative meniscal allografts.

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6 Survival analysis of human meniscal transplantations

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Abstract

We report a prospective survival analysis of 63 consecutive meniscal allografts transplanted into 57 patients. The lateral meniscus was transplanted in 34, the medial meniscus in 17, and both menisci combined in the same knee in 6. For survival analysis we used persistent pain or mechanical damage as clinical criteria for failure. A total of 13 allografts failed (5 lateral, 7 medial and 1 medial and lateral).

A significant negative correlation (p=0.003) was found between rupture of the anterior cruciate ligament (ACL) and succesful meniscal transplantation.

A significant difference (p = 0.004) in the clinical results was found between lateral and medial meniscal transplants.

The cumulative survival rate of the lateral, medial and combined allografts in the same knee, based on the life table method and the Kaplan-Meier calculation is 76%, 50%, and 67%, respectively. The survival of medial meniscal allografts may improve when reconstruction of the ACL is carried out at the same time as meniscal transplantation in an ACL-deficient knee

Introduction

In 1995 we published the preliminary results of human meniscal transplantations with a follow-up of two to five years. [1] The short-term findings showed that meniscal chondrocytes can survive cryopreservation and transplantation by revascularisation of the graft. The results were better in patients with an intact anterior cruciate ligament (ACL) and normal alignment of the knee. After this study we altered our indication for surgery, which are now as follows: a patient under the age of 45 years with pain, disabling compartmental osteoarthitis after total meniscectomy, normal alignment of the knee, and a stable joint. In this study we have sought to determine the survival of meniscal transplants and to establish whether the Knee Assessment Scoring System (KASS) was a useful addition to the Lysholm score.

Patients and Methods

Between 1989 and 1999 we transplanted cryopreserved unmatched human meniscal allografts into 57 patients. All of whom were included in the survival analysis. All had completed a six monthspostoperative rehabilitation programme, except for one whose graft failed four months after operation.

There were 40 men and 17 women with a mean age 39 years (26 to 55). The lateral meniscus was transplanted in 34 patieints, the medial meniscus in 17, and both menisci in the same knee in six. The mean interval between total meniscectomy and transplantation was 16 years (3 to 33) and the mean follow-up was 60 months (4 to 126).

The preoperative planning, collection, preparation, implantation of the allograft and postoperative management were described in detail in 1995.[1] Briefly, an open technique was used to implant the cryopreserved, unmatched meniscal allograft. No bone blocks were used to fix the transplant, and no immunosuppression was given. In this study we changed from non-absorbable to absorbable sutures and reduced the length of hospital stay from ten to seven days.

The clinical criteria for failure of an allograft were; persistent pain, an unsuccesful KASS rsult, a poor Lysholm score, or a detached allograft. According to the KASS, a successful score requires an improvement of at least 10 points or the maintenance of a score of 75 points or higher. The Lysholm score defines excellent as over 94 points, good as 84 to 94 points, fair as 65 to 83 points and poor as less than 65 points. Persistent pain was defined as pain without failure of the allograft. An allograft which failed mechanically was defined as an unsuccesful KASS result, or a poor Lysholm score, with an abnormal allograft which showed tears, or an allograft-capsular detachment at time of second-look arthroscopy. Before 1995, second-look arthroscopies were undertaken after failure and for further investigation. After 1995, they were undertaken only for failure. In a separate study preoperative and postoperative MRI was used to correlate clinical results. Arthroscopy was undertaken in 16 consecutive patients.[2]

For survival analysis we used the clinical criteria for failure using the life-table method and Kaplan-Meier survivorship curves with the SPSS version 9.0 for windows (SPSS Inc., Chicago, Illinois). [3] In one patient who had died, the latest clinical information and radiographs available were assessed. All 57 recipients (63 meniscal allografts) were assessed for survivorship analysis and no patient was lost to follow-up.

Results

We transplanted 63 meniscal allografts into 57 patients. The mean follow-up was 60 months (range 4 to 126). The mean age, the mean time from meniscectomy to

transplantation, and the mean preoperative Lysholm score showed no difference for lateral, medial or combined allografts. Patients with lateral meniscal allografts had a longer mean follow-up compared with those with medial and combined allografts (Table 1).

Both the KASS and Lysholm score identified the same recipients as unsuccesful (KASS) or poor (Lysholm score), and successful (KASS) or excellent, good or fair (Lysholm score). Preoperatively, 21 recipients demonstrated instability, either due to deficiency of the ACL, or post-total meniscectomy laxity. A total of 36 patients had stable knees before and after operation, including four with lateral and two with medial meniscal transplantations which failed with persistent pain. After meniscal transplantation, 11 knees became stable, including one lateral allograft which failed with persistent pain. Ten knees remained unstable, despite transplantation. The postoperative increase in joint stability was significant ($p= 0.001$).

Eight recipients (2 lateral, and 6 medial) had instability of the knee because of deficiency of the ACL. The two lateral allografts were considered successful. Four medial allografts, in combination with rupture of the ACL failed. In two knees, reconstruction of the ACL was undertaken at the same time as medial meniscal transplantation. At follow-up both knees were stable. One was considered to be a failure because of persistent pain, and the second was successful. A significant, negative correlation was found between rupture of the ACL and asuccessful medial meniscal transplantation (paired sample correlation -0.382, $p = 0.003$). One recipient (case 24) who had a combinedi transplantion, died from myocardial infarction 79 months after surgery. A second recipient, again of combined menisci, survived a cerebrovascular infarction 13 months after operation. These death were not considered to be related to meniscal allografting.

No major complications, in the form of peripheral neurovascular lesions, wound infections, haematomas, thrombosis, or joint stiffness occurred. Minor complications developed in five patients because of the use of non-absorbable sutures. They had anterior pain where granulomata had developed around the sutures. These were removed during second-look arthroscopy. Thereafter, absorbable sutures were used and no further granulomata developed. In two patients, a second, minor complication occurred with pain at the site of the portals after second-look arthroscopy. For the second-look arthroscopy we used a central portal through the patellar tendon in order not to compromise the allograft. One recipient became free from pain after infiltration of the portal with local anesthetic and corticosteriods, the other required excision of the scar tissue under local anaethesia.

There was no significant difference in male and female recipients of allografts, but a significant difference was found between the clinical results for lateral

Table 1. Details of meniscal allografts used

Allograft	number of patients	Male	Female (yrs)	mean Age (yrs)	mean Interval* (mths)	mean Follow-up Preop	mean Lysholm score Postop	mean Lysholm score	no. of failures (mths)	mean time of failure
lateral	34	25	9	39 (26-51)	16 (2-27)	70 (12-126)	33 (5 -73)	88 (42-100)	5	53 (24-89)
medial	17	11	6	41 (30-55)	16 (3-33)	45 (4 -108)	39 (15-76)	70 (19-100)	7	25 (4 -38)
combined	6	4	2	40 (31-50)	17 (6-32)	49 (7 -101)	37 (15-56)	77 (48-99)	1	64
Total	57	40	17	39 (26-55)	16 (3-33)	60 (4 -126)	35 (15-56)	80 (19-100)	13	

*time from meniscectomy to transplantation

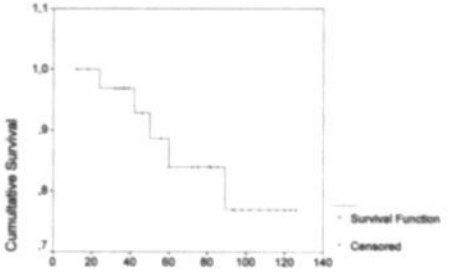

Fig. 1. Survival curve of lateral meniscal allografts

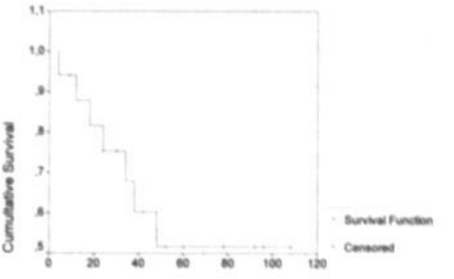

Fig. 2. Survival curve of medial meniscal allografts

and medial meniscal transplants (2-tailed t-test p = 0.004). A comparison between lateral and combined, and medial and combined transplants did not show a significant difference, probably because of the small sample size of the combined group (n=6).

Survival analysis. Using the clinical criteria for failure, 13 patients were considered failure. Lateral meniscal transplantation failed in five, medial in seven and combined transplantation in one. Persistent pain was the cause of failure in eight patients (5 lateral, 2 medial, and 1 combined). The allograft itself failed in five recipients of a medial meniscal allograft, of which four had a rupture of the ACL. Taking the worst case, and clinical criteria for failure, the cumulative survival rate for the lateral allografts was 0.76 (95% confidence interval (CI) 82 to 92), and for the medial 0.50 (95% CI 55 to 83) and for the combined 0.67 (95% CI 58 to 94) (Table 2 - 4). The mean survival time for the lateral, medial and combined tallografts was 111, 69 and 89 months, respectively. Failure of the lateral allografts occurred at a mean of 53 months after surgery and for the medial allografts at a mean of 25 months. The Kaplan-Meier survivorship curve for combined allografts could not be drawn since there was only one valid survival function value per group. Figure 1 and 2 show the Kaplan-Meier survivorship curves when clinical criteria for failure were used for the lateral and medial allografts.

When survival of the allograft was used as an endpoint, the cumulative succes rate for the lateral allografts was 0.88% (95% CI 85 to 92), and 0.63% for the medial allografts (95% CI 55 to 83). The cumulative succes rate for combined allografts did not change.

Table 2. Life table for lateral meniscal allografts

Years since operation	No. of lateral allografts	No. withdrawn	No. at risk	No. of failures	Annual failure rate (%)	Annual success rate (%)	Cumulative success rate (%)
0 to 1	34	0	34	0	0.00	100	100
1 to 2	34	2	33	0	0.00	100	100
2 to 3	32	2	31	1	3.23	96.77	96.77
3 to 4	29	6	26	1	3.85	96.15	93.05
4 to 5	22	2	21	1	4.76	95.24	88.62
5 to 6	19	1	18.5	1	5.41	94.59	83.83
6 to 7	17	4	15	0	0.00	100	83.83
7 to 8	13	3	11.5	1	8.70	91.30	76.54
8 to 9	9	3	7.5	0	0.00	100	76.54
9 to 10	6	3	4.5	0	0.00	100	76.54
10 to 11	3	3	1.5	0	0.00	100	76.54

Table 3. Life table for medial meniscal allografts

Years since operation	No. of lateral allografts	No. withdrawn	No. at risk	No. of failures	Annual failure rate (%)	Annual success rate (%)	Cumulative success rate (%)
0 to 1	17	1	16.5	1	6.06	93.94	93.94
1 to 2	15	0	15	2	13.33	86.67	81.41
2 to 3	13	2	12	2	16.67	83.33	67.85
3 to 4	9	1	8.5	1	11.76	88.24	59.86
4 to 5	7	1	6.5	1	15.38	84.62	50.65
5 to 6	5	1	4.5	0	0.00	100	50.65
6 to 7	4	1	3.5	0	0.00	100	50.65
7 to 8	3	1	2.5	0	0.00	100	50.65
8 to 9	2	1	1.5	0	0.00	100	50.65
9 to 10	1	1	0.5	0	0.00	100	50.65

Table 4. Life table for combined meniscal allografts

Years since operation	No. of lateral allografts	No. withdrawn	No. at risk	No. of failures	Annual failure rate (%)	Annual success rate (%)	Cumulative success rate (%)
0 to 1	6	1	5.5	0	0.00	100	100
1 to 2	5	1	4.5	0	0.00	100	100
2 to 3	4	1	3.5	0	0.00	100	100
3 to 4	3	0	3	0	0.00	100	100
4 to 5	3	0	3	0	0.00	100	100
5 to 6	3	0	3	1	33.33	66.67	66.67
6 to 7	2	1	1.5	0	0.00	100	66.67
7 to 8	1	0	1	0	0.00	100	66.67
8 to 9	1	1	0.5	0	0.00	100	66.67

Discussion

In 1995, we published the preliminary results with follow-up of two to five years of our first 25 meniscal allografts. These are iincluded in this survival analysis. Murray et al stated that survival analysis is a powerful tool for evaluating results, especially when data from patients with different lengths of follow-up are entered and can be withdrawn from the trial at any stage, and for whatever reason. For the analysis it is assumed that all patients had their operation simultanously.[3] Initially, meniscal transplantations were undertaken in arthritic knees which had undergone total meniscectomy. Chondral degeneration grade 4 and malalignment are considered a contraindication for meniscal transplantation. As this and earlier studies have shown, the knee should be stable, or able to be stabilised by appropriate ligament reconstructions.[1]

There is no agreement in the literatuur concerning the most accurate technique for imaging meniscal allografts. Our allografts were sized by radiography of the donor and recipient knees. Pollard et al demonstrated a reproducible radiological relationship between each meniscus and established bony landmarks.[4] Other Tissue Banks use CT or MRI for sizing the allograft and advise that the recipients should be sized by using the same technique. In a study of 12 cadaveric knees which underwent sequential radiographs, MRI and arthrotomy, none of these techniques was sufficiently accurate to measure individual meniscal dimensions. Using less strigent criteria for accuracy, within 5 mm, radiography and MRI became more reliable.[5] The latter is certainly better than radiography in predicting the three-dimensional geometry of the meniscus.[6] The most appropriate, and practical, sizing-technique is currently still based upon measurements on bone. In a study in which 16 patients had a meniscal transplantation matched by radiographs and in which the clinical results were evaluated by MRI and arthroscopy, no mismatch of the size was noted.[2] In our study there were no failures because of mismatch of the allograft. We think that alignment, stability and fixation of the allograft are more important to the clinical result than matching the size.

When the KASS was compared with the Lysholm score, the same patiients were identified as unsuccessful (KASS) or poor (Lysholm score) and successful (KASS) or excellent, good and fair (Lysholm score) The KASS did not add to the Lysholm score. Since the KASS only discriminates between successful and unsuccessful, and the Lysholm score further categorises the successful results into excellent, good and fair, we no longer use the KASS. Although the International Knee Documentation Score (IKDS) is only validated for the evaluation of injuries to knee ligaments we added this score to tour assessment protocol. since there is no validated scoring system to evaluate the results of meniscal surgery, we now use the IKDS in combination with the Lysholm score and consider that this is the best

available scoring system at present. Since pain is considered the major indication for meniscal transplantation, a visual analogue scale for the severity of pain has been added to the protocol. The results for combined transplantation should be interpreted with caution as the number of joints remaining in follow-up is an important variable and determies the reliability of the data. With numbers as low as ten the possible error is of the order of 20%, which is often larger than the cumulative failure rate.[3] Although lesions of the medial meniscus occur three times more frequently than those of the lateral meniscal, we transplanted more lateral than medial allografts. Medial meniscal lesions occur more often because the medial meniscus is firmly attached to the tibia and capsule of the knee, whereas the lateral meniscus has loose peripheral attachments.[7] There are anatomical and functional differences between the lateral and medial meniscus. Levy et al concluded that the medial meniscus is a secondary stabilizer and of more importance to joint stability than the lateral meniscus.[8] The biomechanical interplay between the ACL and the medial meniscus was confired in two recent studies. Both Hollis et al., and Papageorgiou et al. showed that anterior tibial translation and medial meniscal strain were restored to normal levels after reconstruction of the ACL.[9-10] Primary anterior and posterior translations were not affected by lateral meniscectomy before and after resection of the ACL.[11] The lateral meniscus is of more importance to load transmission in the knee. Because of the greater role in stress protection of the lateral meniscus, lateral meniscectomy will be followed by a higher incidence of osteoarthritis compared with medial meniscectomy.[12-14] As pain is a symptom of osteoarthritis, and the main indication for meniscal transplantation, more lateral than medial meniscal allografts were transplanted.

Our study showes that the lateral allografts lasted longer and had fewer failures than the medial allografts. the stability of the knee improved significantly after meniscal translantation, especially when it was caused by anterior translation from total meniscectomy. We agree with Noyes et al. that if anterior laxity is used to describe only anterior translation, it is preferable to use the term anterior translation.[15] Only ten recipients showed still instability after meniscal transplantation, including 5 with deficiency of the ACL.

The difference in the clinical results between lateral and medial allografts can be explained by the anatomical and functional differences between both menisci, and by the difference in frequency of ruture of the ACL in both groups. Only two recipients of a lateral allograft had a ruture of the ACL which did not impair the clinical result. By contrast, six recipients of medial allografts had rupture of the ACL with significant impairment in the clinical outcome. The reason for failure was instability because of deficiency of the ACL, leading to secondary detachment of the allograft. Two patients with a failed medial meniscal allograft

had a second medial meniscal transplant. This was combine with an autogenous bone-patellar tendon-bone ACL reconstruction. At follow-up, both knees were stable. One was considered to be a success and the other a failure because of persistent pain. Several studies on meniscal repair have shown that meniscal healing occurs in up to 96% of stable joints, and that the results are significantly worse in ACL-deficient knees.[16-19] There is no distinction made between lateral and medial meniscal repair. As with meniscal allografts there could, perhaps, be a significant difference between the results of lateral and medial meniscal repair in an ACL-deficient knee.

Our preliminary results at follow-up at two to five years showed that the results were better in knees with an intact ACL and a normal alignment of the joint.[1] Since 1995, meniscal allografts have been transplanted only in knees with an intact ACL and normal alignment. In two cases we transplanted a medial meniscal allograft in combination with reconstruction of the ACL.

In this study, the results after lateral meniscal transplantation are satisfactory. A significant negative correlation was found between rupture of the ACL and a successful transplantation. The survival of medial meniscal transplantation will improve when meniscal transplantation is undertaken at the same time as reconstruction of the ACL in an ACL-deficient knee. Anterior tibial translations and strain on the medial meniscal allograft will then be reduced to levels of an intact knee.[9,,10]

Although the same technique was used to transplant medial and lateral allografts, the results were significantly different. This can be explained by the differences in anatomy, biomechanical function, and subsequently by the differences in frequency of these mensical lesions, ruptures of the ACL and the incidence of postmeniscectomy osteoarthritis. It is thus not possible to compare the results of lateral and medial meniscal allografts.

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7 Summary, general discussion and future research

This thesis describes the value of meniscal transplantation and shows the first long term results of this new evolving technique. The meniscal transplantations were not compared with a group of controle patients, treated with non-transplantation techniques. To design such a prospective randomised controle trail the problem will rise that in the patient in which a meniscal transplantation is indicated, no other treatment options are available. They are to young for a knee arthroplasty and an osteotomy is not indicated because alignment should be neutral. Some patients in this study had the advise to arthrodese the knee joint.

Except for meniscectomy this thesis does not describe prognostic factors for the development of osteoarthritis of the knee. It is known that there is a genetic predisposition to develop osteoarthritis. Other prognostic factors are obesity, physical activity, previous knee injury and Heberden's nodes. The latest is associated with patellofemoral osteoarthritis, whereas the other factors are stronger correlated with tibiofemoral osteoarthritis.

In **Chapter 1** anatomical and biomechanical aspects of the native meniscus are described. There are anatomical and biomechanical differences between the lateral and medial meniscus. Although lesions of the medial meniscal occur three times more frequently than those of the lateral meniscal, the incidence of osteoarthritis after lateral meniscectomy is higher, and subsequently the incidence of pain after lateral meniscectomy is also higher. The medial meniscus is of more importance to joint stability, whereas the lateral meniscus is of more importance to load distribution.

When a meniscus is torn in the vascular zone, meniscal repair can be indicated, especially in a longitudinal or bucket handle lesion. In most of the cases arthroscopic partial meniscectomy is advised. When there is pain and compartmental osteoarthritis after (sub)total meniscectomy, meniscal replacement may be indicated.

The present study was performed to determine if the progression of degenerative changes in the knee joint after total meniscectomy could be delayed or even stopped by meniscal transplantation. To achieve this long-term objective, the meniscal allograft has to grow to the knee capsule to perform the biomechanical function in the knee, without an inflammatory response, and pain and disability should improve significantly. These improvements should result in significantly better postoperative clinical scores, without deterioration of radiological and arthroscopic criteria, and of the histological and laboratory findings. The rationale, prerequisites and technique of meniscal transplantation are described.

In **Chapter 2** the preliminary results at follow-up of two to five years of the first 25 meniscal allografts are shown. The technique of meniscal transplantation is described, using no bone blocks. Immunosuppression is not given. The conclusion is that meniscal chondrocytes can survive cryopreservation and transplantation. Ingrowth of the allograft to the knee capsule occurs, and the results are better in a stable joint with a normal alignment.

MRI has an established role in the diagnosis of meniscal pathology. The role of MRI in the postoperative evaluation after meniscal repair and transplantation is less clear. In **Chapter 3** it is shown that arthroscopy correlated better to clinical results than MRI. With highly sophisticated MRI techniques, a more significant correlation could be expected. The study provides definitions to evaluate meniscal allografts with arthroscopy and MRI.

Intact articular cartilage is thought to be immunogenetically privileged tissue to transplant. It does not contain a load of marrow-derived cells, and the matrix prevents exposure of chondrocytes. Little is known about the immune response after meniscal transplantation. Therefore the presence of antibodies against human leukocyte antigens (HLA) in recipients of cryopreserved, non-tissue-antigen-matched human meniscal allografts was evaluated. The results are shown in **Chapter 4**; 11 out of 18 male recipients, with no history of prior transplantation or blood transfusion, became sensitized. Whether this is a positive sign, theoretically the immune response can induce ingrowth of recipient synovial cells in the meniscal allograft, must be studied in more detail through more specific analyses to reveal the anti-HLA reactivity. In **Chapter 5** a study concerning red blood cells is described. 32 patients were evaluated pre- and postoperatively for the presence of irregular erythrocyte antibodies (IEA) in recipients of meniscal allografts. No new IEA's were detected postoperatively, including 6 Rhesus-D negative patients who received a Rhesus-D positive meniscal allograft. Nevertheless, when unprocessed bone plugs are used to fix the meniscus, it is recommended to give women of childbearing age who are Rhesus-D negative only Rhesus-D negative meniscal allografts.

In **Chapter 6** a prospective survival analysis of 63 consecutive meniscal allografts transplanted into 57 patients is described. The clinical results and the survival of lateral meniscal transplantations were better than for the medial allografts. The differences in clinical results and survival can be explained by differences anatomy, biomechanical function, and subsequently by the difference of these meniscal lesions, ruptures of the ACL, and the incidence of postmeniscectomy osteoarthritis. It is thus not possible to compare the resutls of lateral and medial meniscal allografts. And it could be possible that the best technique to secure the allograft is different for the lateral and the medial meniscus.

In conclusion, it can be stated that no deterioration or improvement of articular cartilage after meniscal transplantation was objectified, but ingrowth of the allograft to the knee capsule was shown. Clinical results and survival were good for the lateral, intermediate for both in the same knee and poor for the medial allografts. The results in the medial meniscal transplant will improve if instability in the knee is treated at the same time.

Only a subtle immune response and no irregular erythrocyte antibodies were found after meniscal transplantation. Recipients of a meniscal allograft can become sensitized, because antibodies against human leukocyte antigens were found after transplantation. This subtle immune response may induce the phenomenon of creeping substitution and incorporation and revascularisation of the graft.

Concerning the evaluation of meniscal transplants it can be concluded that there is no specific scoring system to evaluate the meniscus. There are only validated scoring systems for ligament reconstruction and prosthesis in the knee joint. To enable comparability of meniscal transplantation studies, in the absence of a meniscal scoring system, the clinical evaluation protocol should contain at least the Lysholm, and the International Knee Documentation Score, a Visual Analogue Scale for pain, and a standard and full standing X-ray of the knee joint. Unless sophisticated MR imaging techniques are used, arthroscopy correlates best to the clinical results.

Concerning the indication for meniscal transplantation it can be stated that, although contact pressure on articular cartilage is reduced after meniscal transplantation, there is no evidence in animal and human studies that meniscal transplantation protects articular cartilage after meniscectomy. Therefore transplantation of a meniscal allograft is not indicated to prevent articular cartilage degeneration after (sub)total meniscectomy; it is not a prophylactic procedure to prevent osteoarthritis.

Meniscal transplantation is indicated in a knee with disabling compartmental pain, after (sub)total meniscectomy, in a patient under the age of 45 years. Articular cartilage should not have deteriorated severely, and the knee joint should

be stable, and should have a normal alignment.
After this thesis, interesting areas for further study remain. The specific purpose of further study could be:

1. To assess in more detail why recipients of meniscal allografts can become sensitized. Therefore specific analysis (particularly for HLA class 2) to confirm the anti-HLA reactivity is recommended.
2. To assess which fixation technique of meniscal allografts provides the best results. Because the medial meniscus is firmly attached, and the lateral meniscus is more loosely attached to the knee capsule, different fixation techniques might be needed for medial and lateral allograft transplantation. Biomechanical studies and dynamic studies in an open MR imaging setting should give the answers.
3. A prospective DNA fingerprinting study should provide the answer if incorporation of the meniscal allograft takes place by the phenomenon of creeping substitution.
4. To assess the importance of sizing of the allograft .
5. To investigate if it is possible to culture a meniscus with the same biomechanical properties as a native meniscus with tissue engineering techniques. If this is possible the potential risk of disease transmission is eliminated, and the resources of allografts unlimited.
6. To develop more accurate methods to assess and document meniscal surgery, including resection, repair and transplantation, and the effects on articular cartilage and the knee joint.
7. A specific scoring system to evaluate the meniscus after meniscectomy, meniscal repair and meniscal transplantation has to be developed.

Samenvatting

Dit proefschrift beschrijft de waarde van meniscustransplantatie en laat de eerste lange termijn resultaten zien. De meniscustransplantatie patienten zijn niet vergeleken met een controle groep. Bij het opzetten een prospectief gerandomiseerde studie doet zich het probleem voor dat bij de patienten waar een meniscustransplantatie geindiceerd is er geen andere behandelingsopties zijn. Ze zijn te jong voor een totale of hemi knie prothese. En omdat de been as neutraal is, is een tibiakop osteotomie niet geindiceerd. Het advies dat enkele patienten uit deze serie eerder hadden gekregen was een kniearthrodese.

Behoudens meniscectomie gaat dit proefschrift niet in op de prognostische factoren voor het ontstaan van arthrose in de knie. Het is bekend dat er een genetische predispositie is voor het ontstaan van arthrose. Andere prognostische factoren zijn; overgewicht, fysieke activiteit, eerder knie letsel en noduli van heberden. Deze laatste zijn geassocieerd met het ontstaan van patellofemorale arthrose, terwijl de andere factoren sterker met tibiofemorale arthrose zijn gecorreleerd.

In **hoofdstuk 1** worden de anatomische en biomechanische aspecten van de meniscus beschreven. Ook wordt ingegaan op de verschillen tussen de laterale en mediale meniscus. Terwijl letsels aan de mediale meniscus drie keer zo frequent voorkomen ten opzichte van de laterale meniscus, is de incidentie van arthrose na laterale meniscectomie hoger, met als gevolg een hogere incidentie van pijn na laterale meniscectomie. De mediale meniscus is van meer belang voor de stabiliteit van de knie, terwijl de laterale meniscus van meer belang is voor de overdracht van het lichaamsgewicht op het onderbeen.

Wanneer een meniscus in het vasculaire gedeelte is gescheurd, kan deze worden gehecht, zeker wanneer het een longitudinale of "bucket handle" scheur betreft. Echter, in de meeste gevallen is arthroscopische partiële mediale meniscectomie te adviseren. Is er na een (sub)totale meniscectomie pijn, in het betreffende compartiment van de knie ontstaan, dan kan meniscustransplantatie geindiceerd zijn.

De huidige studie is uitgevoerd om te onderzoeken of het ontstaan van de degeneratieve afwijkingen, na totale meniscectomie, gestopt dan wel vertraagd kan worden, door een meniscustransplantatie. Om dit fenomeen op de lange termijn te kunnen aantonen, is een eerste vereiste dat de donormeniscus vastgroeit aan het kniekapsel en zo de biomechanische funktie in de knie kan vervullen. Tevens behoren dan pijnvermindering en funktieverbetering op te treden, zonder dat er een afstotingsreactie geinduceerd wordt. De pijnvermindering en funktieverbetering moeten een significante verbetering van de postoperatieve klinische scores geven. De radiologische en arthroscopische criteria, en de laboratorium - en histologische bevindingen, moeten geen verslechtering laten zien. De ratio, de voorwaarden en verschillende technieken van meniscustransplantatie worden in **hoofdstuk 1** beschreven.

In **hoofdstuk 2** worden de eerste resultaten bij 23 patienten met een follow-up van 2 tot 5 jaar weergegeven. De meniscustransplantatie techniek wordt beschreven. Er wordt geen gebruik gemaakt van botpluggen die aan de donormeniscus vastzitten voor de fixatie van het transplantaat in de knie. Immunosuppressiva worden niet toegediend. De conclusie is dat de meniscuschondrocyten zowel de conservering als de transplantatie overleven. Ook groeit de donormeniscus aan het kniekapsel vast. De klinische resultaten zijn beter wanneer de knie stabiel is en een normale beenas heeft.

Bij de diagnostiek van meniscusletsels heeft de magnetic resonance imaging (MRI) een bewezen waarde. De waarde van de MRI bij de postoperatieve beoordeling van gehechte en getransplanteerde menisci is minder duidelijk. Dat de arthroscopie beter correleert met de klinische resultaten dan de MRI wordt aangetoond in **hoofdstuk 3**. Met meer geavanceerde MRI technieken mag een betere correlatie worden verwacht. In deze studie worden ook definities voor de arthroscopische en MRI beoordeling van getransplateerde menisci gegeven.

Men veronderstelt dat intakt gewrichtskraakbeen immunologische gezien bevoorrecht weefsel is om te transplanteren. Het bevat geen beenmergcellen en de kraakbeenmatrix voorkomt dat chondrocyten aan een immunologische reactie worden blootgesteld. Om die reden werd de aanwezigheid van antilichamen tegen het humane leukocyten antigeen (HLA), bij de ontvangers van een gecryopreserveerde, niet weefselantigeen gematched menselijke donormenisci, onderzocht. De resultaten staan beschreven in **hoofdstuk 4**; 11 van de 18 mannelijke ontvangers, die geen eerdere transplantatie of bloedtransfusie hadden gekregen, bleken te zijn gesensibiliseerd. Het is onduidelijk of dit een gustig teken is. Theoretisch zou de immuunreactie ingroei van synoviale cellen in de donormeniscus kunnen stimuleren. Specifiekere analyse van de HLA-reactiviteit zou dit gedetaileerder kunnen beschrijven.

In **hoofdstuk 5** wordt naar de rode bloedcellen gekeken. Bij 32 ontvangers van een donormeniscus werd pre-en postoperatief de aanwezigheid van irregulaire antilichamen van de erythrocyten (IEA) bepaald. Nieuwe IEA's werden postoperatief niet waargenomen. Ook niet bij de 6 resus-d negatieve ontvangers die een resus-d positieve donormeniscus hadden ontvangen. Omdat na bottransplantatie wel IEA's zijn aangetoond, is het te adviseren om vrouwen die nog in de vruchtbare leeftijd zijn, en die resus-d negatief zijn, een resus-d negatieve donormeniscus te geven, zeker wanneer botpluggen ter fixatie van de donormeniscus worden gebruikt.

De resultaten op de lange termijn worden in **hoofdstuk 6** weergegeven in een prospectieve survival analyse van alle 63 donor menisci die bij 57 patienten werden getransplanteerd. De klinische resultaten en de overleving van de laterale menisci waren beter dan die van de mediale. De verschillen in klinische resultaten en overleving kunnen verklaard worden door de verschillen in anatomie en funktie van de mediale en laterale meniscus. Door deze verschillen kunnen de resultaten van de mediale en laterale meniscustransplantaten niet met elkaar vergeleken worden. Het zou zelfs zo kunnen zijn dat de beste techniek om de donormeniscus te fixeren verschilt voor het mediale en laterale compartiment van de knie.

In **hoofdstuk 7** worden de beschreven studies samengevat en gerelateerd aan de gegevens uit de literatuur. Nieuwe ideeën voor studies, zijn ook weergegeven.

Geconcludeerd kan worden dat er na een meniscustransplantatie geen verslechtering of verbetering van het gewrichtskraakbeen geobjectiveerd kan worden. Wel is aangetoond dat de donormeniscus aan het gewrichtskapsel vastgroeit. De klinische resultaten en overleving van de laterale meniscustransplantatie zijn goed. Deze zijn gemiddeld als zowel de mediale als de laterale meniscus in dezelfde knie worden getransplanteerd. Wanneer enkel de mediale meniscus wordt getransplanteerd zijn deze slecht. De slechte resultaten worden verklaard door de hoge incidentie aan voorste kruisbandrupturen in de groep met mediale meniscustransplantaten. De resultaten van de transplantatie van de mediale meniscus zullen verbeteren wanneer de voorste kruisbandinstabiltiteit gelijktijdig met de meniscustransplantatie wordt behandeld.

Na meniscustransplantatie werd alleen een subtiele immuun respons waargenomen. Er werden geen nieuwe irregulaire erythrocyten antilichamen aangetoond. HLA-sensibilisatie daarentegen is wel opgetreden na donormeniscustransplantatie. Deze immunologische respons kan het fenomeen van voortschrijdende vervanging (creeping substitution), incorporatie en revascularisatie ingang zetten. Dat er geen specifiek meniscus-scoringssysteem is bemoeilijkt de onderlingen vergelijking van verschillende meniscustransplantatiestudies. Er bestaan alleen sco-

ringssystemen voor ligamentaire reconstructies en prothesen in de knie. Om beter verschillende meniscustransplantatie onderzoeken te kunnen vergelijken, terwijl er nog geen meniscus scoringssysteem is, moet het evaluatieprotocol zeker de Lysholm score, de International Knee Documentation Score (IKDS), een Visuale Analogue Scale (VAS)-score voor de pijn bevatten. Een standaard röntgenfoto van de knie en een staande been opname zijn ook noodzakelijk. Wanneer meer geavanceerde MRI systemen worden gebruikt zal een betere correlatie met de klinische en arthroscopische bevindingen ontstaan.

Met betrekking tot de indicatie voor een meniscustransplantatie kan gesteld worden dat, ondanks dat de contactdruk op het gewrichtskraakbeen door transplantatie wordt gereduceerd, er geen bewijs bij mens en dier is dat meniscustransplantatie een beschermend effect heeft op het gewrichtskraakbeen. Om die reden is een meniscustransplantatie niet geindiceerd als profilactische behandeling tegen het ontstaan van degeneratieve veranderingen van het gewrichtskraakbeen na een (sub)totale meniscectomie.

De belangrijkste indicatie voor een meniscustransplantatie is pijn na (sub)totale meniscectomie, bij patienten die jonger zijn dan 45 jaar. De pijn moet een invaliderend karakter hebben, de mate van arthrose moet niet te ver gevorderd zijn. Daarnaast moet de knie stabiel zijn en een normale beenas hebben.

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Curriculum vitae

Ewoud van Arkel werd geboren op 5 oktober 1958 in Utrecht. Na het behalen van het VWO-examen aan het Herman Jordan Montessori Lyceum te Zeist werd in 1980 begonnen met de studie geneeskunde aan de Rijksuniversiteit Utrecht. Het artsexamen werd in januari 1989 behaald.

In 1989 begon hij als arts-assistent niet in opleiding in het Zeister Algemeen Ziekenhuis (nu Lorentz Ziekenhuis) op de afdeling Chirurgie en Orthopaedie. Daarna volgde hij in 1990 een AGNIO-schap op de afdeling Algemene Heelkunde van het Westeinde Ziekenhuis te Den Haag (hoofd: dr R.K.J. Koumans).

De basis voor dit proefschrift werd gelegd in 1991 tijdens zijn AGNIO-schap Orthopaedie in het de Wever Ziekenhuis te Heerlen (nu Atrium Medisch Centrum Heerlen, opleider dr. A.J. Tonino).

De vooropleiding Algemene Heelkunde werd van 1992 tot 1994 gevolgd in het Academisch Ziekenhuis Maastricht (opleider: Prof dr. G Kootstra). Ter overbrugging van de tijd tussen de vooropleiding en de opleiding orthopaedie werd in 1994 een stage gelopen bij A.E. Gross in het Mount Sinai Hospital te Toronto, Canada.

De opleiding Orthopaedie werd gestart onder leiding van dr A.J. Tonino in het Atrium Medisch Centrum Heerlen. De stage kinderorthopaedie en rugchirurgie werd gevolgd in het Academisch Ziekenhuis Maastricht (opleider: Prof dr. R Geesink).

Op 1 juni 1998 werd hij geregistreerd als Orthopaedisch Chirurg. Sindsdien is hij werkzaam in de Maatschap Orthopaedie Westeinde Ziekenhuis van het Medisch Centrum Haaglanden, in associatie met dr. F.P. Bernoski and
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