REFERENCES TO CHONDROCYTE STIMULATION IN THE CURRENT LITERATURE

1. Adams CS, Horton WE Jr. Laboratory of Biological Chemistry, Gerontology Research Center, National Institute on Aging, National Institutes of Health, Baltimore, Maryland, USA. **Chondrocyte apoptosis increases with age in the articular cartilage of adult animals**. *Anatomical Record.* 250(4):418-25, 1998 Apr.

Abstract

BACKGROUND: Apoptosis in vivo has been identified in developing cartilage from embryonic chick sterna and avian and murine growth plates. To date, no evidence exists that chondrocytes in articular cartilage undergo apoptosis. METHODS: We examined the distribution of cells demonstrating fragmented DNA in the articular knee cartilage of C57BL/6 mice (aged 11, 18, 24, and 30 months) and Wistar rats (aged 6, 12, and 24 months) using a DNA end-labeling technique. RESULTS: Control experiments utilizing retinoic acid-induced apoptosis in a chondrocyte cell line, established that DNA end-labeling correlated with DNA ladder formation. In vivo, apoptotic cells were detected in articular cartilage tissue in both species examined. The percentage of apoptotic cells increased significantly ($P < 0.05$ with age) for all joint surfaces in both species. No significant difference was found between the medial and lateral or femoral and tibial joint surfaces of the knee. Apoptotic cells were observed in both the calcified and uncalcified regions of the articular cartilage of C57 mice. In the rat, only the calcified region of articular cartilage contained apoptotic cells. CONCLUSIONS: These results suggest that apoptosis plays a role in some aspect of maintenance, remodeling, or turnover of mature articular cartilage. In addition, the increase in apoptosis associated with aging could contribute to the greater risk for cartilage degeneration.

2. Bahuaud J, Maitrot RC, Bouvet R, Kerdiles N, Tovagliaro F, Synave J, Buisson P, Thierry JF, Versier A, Romanet JP, Chauvin F, Gillet JP, Allizard JP, de Belenet H. Service de chirurgie orthopedique-traumatologique de: hopital d'instruction des armees (HIA) Robert-Picque, Villenave-d'Ornon, France. **[Implantation of autologous chondrocytes for cartilagenous lesions in young patients. A study of 24 cases].** [French] *Chirurgie.* 123(6):568-71, 1998 Dec.

Abstract

STUDY AIM: The aim of this study was to describe the treatment of symptomatic knee cartilage defects on young active patients by autologous chondrocyte implantation and to report preliminary results in 24 patients. PATIENTS AND METHODS: Since April 1996, 24 selected patients underwent 25 implantations in five military hospitals. There were 19 men and five women (all of them practicing sports); mean age was 27. Lesions were localized on left (n = 13) and right (n = 12) aligned and stabilized knees. There were 12 isolated cartilage defects (eight OCD and four posttraumatic) and 13 associated with ligament lesions (n = 8) or multiple and severe lesions (n = 3 indication of salvage). Mean surface of cartilage defects was 6 cm2. Mean preoperative evolution was 11 months and stage was grade IV (Outerbridge) for all. The first step was arthroscopy for classification and biopsy. The second one was implantation after a 3-week delay (for the ex vivo culture) through arthrotomy, under a periosteal flap taken from tibia and sutured on the edges of the prepared defect. Weight bearing was allowed after the 6th week; MRI was performed at 6, 12, 18, 24 months. The follow up was evaluated with three scales: Lysholm 2, Tegner Activity, Cincinnati Knee Rating System. RESULTS: Postoperative complications included: algodystrophy (n = 2) and phlebitis (n = 1). Four patients were revised at 6 months, seven between 6 and 12 months, 11 after. The longest follow-up was 26 months. Results were poor in one patient (salvage). For the others, pain and swelling decreased after 6 months and disappeared after 12 months. CONCLUSION: Autologous chondrocyte implantation used in this series and in a large international ongoing series seems to be the only procedure allowing a true long-term regeneration of cartilage defects. Some questions remain, on the biological level in relation with the use of some growth factors and the risk of chromosomic abnormalities, and on the economical level because of the high cost of this technique.

3. Behrens P, Ehlers EM, Kochermann KU, Rohwedel J, Russlies M, Plotz W. Orthopadischen Klinik, Med. Univ. zu Lubeck. **[New therapy procedure for localized cartilage defects. Encouraging results with autologous chondrocyte implantation].** [German]. *MMW Fortschritte der Medizin*. 141(45):49-51, 1999 Nov 11.

Abstract

Owing to the poor regenerative capacity of cartilage, cartilaginous defects are considered to represent pre-arthrotic factors. In addition to autologous and allogenic osteochondral fragments, proliferative tissue, such as periosteum and perichondrium are increasingly being used as graft material. The aim of treatment is to eliminate the defect and to restore the load-bearing capacity and function of the affected joint. A new, recently introduced, approach aims to stimulate the formation of new cartilage via autologous cultured chondrocyte implantation (ACI). The rationale for this treatment is the restoration of loadable hyaline or hyaline-like articular cartilage. Although long-term results are not yet available, clinical follow-up data obtained so far are encouraging. In addition to existing methods of treating cartilaginous defects, this article describes a modified method of transplantation of autologous chondrocytes. With this method the periosteal flap used to cover a defect is replaced by an

absorbable collagenI/III membrane (Chondrogide, Geistlich Wolhusen, Switzerland) that is used as a carrier for the patient's own chondrocytes. After placement in the defect, the membrane is fixed in place with fibrin glue (MACI).

4. Bradham DM, Horton WE Jr. Laboratory of Biological Chemistry, National Institute on Aging, National Institutes of Health, Baltimore, MD, USA. **In vivo cartilage formation from growth factor modulated articular chondrocytes**. *Clinical Orthopaedics & Related Research*. (352):239-49, 1998 Jul.

Abstract

Recent procedures for autologous repair of cartilage defects may be difficult in elderly patients because of the loss of stem cells and chondrocytes that occurs with age and the slow in vitro proliferation of chondrocytes from aged cartilage. In this study secondary chondroprogenitor cells were obtained by modulating the phenotype of articular chondrocytes with growth factors and stimulating the proliferation of these cells in culture. Chondrocytes isolated from the articular cartilage of mature New Zealand White rabbits were exposed to a combination of transforming growth factor beta and basic fibroblast growth factor treatment. These cells ceased the production of Collagen II (a marker for the chondrocyte phenotype) and underwent a 136-fold increase in cell number. Next, the cells were placed in high density culture and reexpressed the chondrocyte phenotype in vitro and formed hyaline cartilage in an in vivo assay. Primary chondrocytes obtained from articular cartilage of elderly humans could be manipulated in a similar fashion in vitro. These human secondary chondroprogenitor cells formed only cartilage tissue when assayed in vivo and in tissue bioreactors. This approach may be essential for autologous repair of degenerated articular cartilage in elderly patients with osteoarthritis.

5. Brittberg M. Bone and Cartilage Research, Research Centre for Endocrinology and Metabolism, Goteborg University, Sweden. **Autologous chondrocyte transplantation**. [Review] [38 refs]. *Clinical Orthopaedics & Related Research*. (367 Suppl):S147-55, 1999 Oct.

Abstract

The intrinsic capacity of cartilage to repair chondral injuries is poor. Different techniques to induce cartilage repair with the use of extrinsic chondrogeneic cell sources have been explored in experimental models. Cells can be harvested autologously or as allografts from a healthy part of the donor tissue, isolated, expanded in vitro, and finally implanted into the defect in high densities. Pure chondrocytes, epiphyseal or mature, allogeneic or autologous, and other types of mesenchymal cells have been used. The composition and structure of the extracellular cartilage matrix are maintained through a balance of anabolic and catabolic activities controlled by the unique chondrocytes. They keep the cartilage alive; they alone maintain it and regulate it. It therefore seems important to use true committed chondrocytes to repair a local cartilaginous defect. The rational basis for the use of committed autologous chondrocytes in combination with a covering periosteal membrane in the treatment of deep cartilage defects is presented. [References: 38]

6. Buckwalter JA, Mankin HJ. Department of Orthopaedics, University of Iowa, Iowa City, USA. **Articular cartilage: tissue design and chondrocyte-matrix interactions**. [Review] [78 refs]. *Instructional Course Lectures*. 47:477-86, 1998.

Abstract

The unique biologic and mechanical properties of articular cartilage depend on the design of the tissue and the interactions between the chondrocytes and the matrix that maintain the tissue. Chondrocytes form the macromolecular framework of the tissue matrix from three classes of molecules: collagens, proteoglycans, and noncollagenous proteins. Type II, IX, and XI collagens form a fibrillar meshwork that gives the tissue as form and tensile stiffness and strength. Type VI collagen forms part of the matrix immediately surrounding the chondrocytes and may help the chondrocytes to attach to the macromolecular framework of the matrix. Large aggregating proteoglycans (aggrecans) give the tissue its stiffness to compression and its resilience and contribute to its durability. Small proteoglycans, including decorin, biglycan, and fibromodulin, bind to other matrix macromolecules and thereby help to stabilize the matrix. They may also influence the function of the chondrocytes and bind growth factors. Anchorin CII, a noncollagenous protein, appears to help to anchor chondrocytes to the matrix. Cartilage oligomeric protein may have value as a marker of turnover and degeneration of cartilage, and other noncollagenous proteins, including tenascin and fibronectin, can influence interactions between the chondrocytes and the matrix. The matrix protects the cells from injury due to normal use of the joint, determines the types and concentrations of molecules that reach the tells and helps to maintain the chondrocyte phenotype. Throughout life, the tissue undergoes continual internal remodeling as the cells replace matrix macromolecules lost through degradation. The available evidence indicates that normal matrix turnover depends on the ability of chondrocytes to detect alterations in the macromolecular composition and organization of the matrix, including the presence of degraded molecules, and to respond by synthesizing appropriate types and amounts of new molecules. In addition, the matrix acts as a signal transducer for the cells. Loading of the tissue due to use of the joint creates mechanical, electrical, and physicochemical signals that help to direct the synthetic and degradative activity of chondrocytes. A prolonged severe decrease in the use of the joint leads to alterations in the composition of the matrix and eventually to loss of tissue structure and mechanical

properties, whereas use of the joint stimulates the synthetic activity of chondrocytes and possibly the internal tissue remodeling Aging leads to alterations in the composition of the matrix and the activity of the chondrocytes, including the ability of the cells to respond to a variety of stimuli such as growth factors. These alterations may increase the probability of degeneration of the cartilage. [References: 78]

7. Carver SE, Heath CA. Department of Chemical Engineering, Iowa State University, Ames, Iowa 50011-2230, USA. **Increasing extracellular matrix production in regenerating cartilage with intermittent physiological pressure.** *Biotechnology & Bioengineering*. 62(2):166-74, 1999 Jan 20.

Abstract

Isolated equine chondrocytes, from juveniles and adults, were cultured in resorbable polyglycolic acid meshes for up to 5 weeks with semicontinuous feeding using a custom-made system to intermittently compress the regenerating tissue. Assays of the tissue constructs indicate that intermittent compression at 500 and 1000 psi (3.44 and 6.87 MPa, respectively) stimulated the production of extracellular matrix, enhancing the rate of de novo chondrogenesis. Constructs derived from juvenile cells contained concentrations of extracellular matrix components at levels more like that of native tissue than did constructs derived from adult cells. With intermittent pressurization, however, even adult cells were induced to increase the production of extracellular matrix. At both levels of intermittent pressure, the concentration of sulfated glycosaminoglycan in constructs from juvenile cells was found to be up to ten times greater than concentrations in control (nonpressurized) and adult cell-derived constructs. Whereas collagen concentrations in the 500 psi and control constructs were not significantly different for either juvenile or adult cell-derived constructs, intermittent pressurization at 1000 psi enhanced the production of collagen, suggesting that there may be a minimum level of pressure necessary to stimulate collagen formation. Copyright 1999 John Wiley & Sons, Inc.

8. Chen AC, Nagrampa JP, Schinagl RM, Lottman LM, Sah RL. Department of Bioengineering, University of California, San Diego, La Jolla 92093-0412, USA. **Chondrocyte transplantation to articular cartilage explants in vitro**. *Journal of Orthopaedic Research*. 15(6):791-802, 1997 Nov.

Abstract

The transplantation of chondrocytes has shown promise for augmenting the repair of defects in articular cartilage. This in vitro study examined the efficiency of the transplantation of bovine chondrocytes onto articular cartilage disks and the ability of the transplanted chondrocytes to subsequently synthesize and deposit proteoglycan. The radiolabeling of chondrocyte cultures with [3H]thymidine, followed by 4 days of chase incubation, resulted in the incorporation of 98% of the radiolabel into DNA (as assessed by susceptibility to DNase). At the end of the culture period, the [3H]DNA was stable, with a half-life of radioactivity loss into the medium of 73 days. With use of radiolabeled chondrocytes for quantitation, the efficiency of transplantation onto a cartilage substrate was 93 +/- 4% for seeding densities of as much as 650,000 cells per cm2 and a seeding duration of 1 hour. These findings were confirmed both by tracking cells stained with 5-chlormethylfluorescein diacetate and by quantitating DNA. During the 16 hours after seeding onto a cartilage substrate (in which the endogenous cells had been lysed by lyophilization), the transplanted cells synthesized sulfated proteoglycan in direct proportion to the number of cells seeded. Most (83%) of the newly synthesized proteoglycan was released into the medium rather than retained within the layer of transplanted cells and the recipient cartilage substrate. Comparative studies with lyophilized-rehydrated or live cartilage as the recipient substrate indicated a similar efficiency of chondrocyte seeding and proteoglycan synthesis by the seeded chondrocytes. The transplanted cells retained the chondrocyte phenotype, as judged by a high proportion of the [35S]macromolecules being in the form of aggrecan that was capable of aggregating with hyaluronan and link protein, as well as by immunostaining within and around the transplanted cells for type-II, but not type-I, collagen. These results indicate that the number of chondrocytes transplanted onto a cut cartilage surface greatly affects the level of matrix synthesis; this in turn may affect repair.

9. Duchow J, Hess T, Kohn D. Orthopadische Universitatsklinik, Universitat des Saarlandes, Homburg Saar, Germany. **Primary stability of press-fit-implanted osteochondral grafts. Influence of graft size, repeated insertion, and harvesting technique.** *American Journal of Sports Medicine*. 28(1):24-7, 2000 Jan-Feb.

Abstract

The aim of this study was to evaluate the fixation strength of press-fit-implanted osteochondral grafts with respect to graft size (length and diameter), the effect of repeated insertion after pullout, and harvesting technique. Experiments were performed using the Osteochondral Autograft Transfer System on porcine femoral condyles. Failure loads of 10-mm-long grafts (mean, 47 N) were significantly lower than failure loads of 15-mm-long grafts (mean, 93 N) and 20-mm-long grafts (mean, 110 N) (all grafts, 11 mm in diameter). Reinsertion of the 15-mm-long grafts after initial pullout resulted in a significant reduction of failure loads (mean, 93 N versus 44 N). Failure loads of 8-mm-diameter grafts (mean, 41 N) were significantly lower than those of 11-mm-diameter grafts (mean, 92 N) (all 15 mm long). Levering of the tubular chisel during graft harvest significantly decreased press-fit stability as compared with simple turning of the chisel (mean, 32 N versus 52 N) (8-mm diameter and 15-mm length). These results

suggest that primary fixation strength of press-fit-inserted osteochondral grafts depends on the size of the grafts and that repeated pullout and reinsertion of grafts as well as a nonoptimal harvesting technique (levering) will reduce primary stability.

10. Durrant LA, Archer CW, Benjamin M, Ralphs JR. Connective Tissue Biology Laboratory, Cardiff School of Biosciences, Cardiff University, UK. **Organisation of the chondrocyte cytoskeleton and its response to changing mechanical conditions in organ culture.** *Journal of Anatomy*. 194 (Pt 3) :343-53, 1999 Apr.

Abstract

Articular cartilage undergoes cycles of compressive loading during joint movement, leading to its cyclical deformation and recovery. This loading is essential for chondrocytes to perform their normal function of maintenance of the extracellular matrix. Various lines of evidence suggest the involvement of the cytoskeleton in load sensing and response. The purpose of the present study is to describe the 3-dimensional (3D) architecture of the cytoskeleton of chondrocytes within their extracellular matrix, and to examine cytoskeletal responses to experimentally varied mechanical conditions. Uniformly sized explants of articular cartilage were dissected from adult rat femoral heads. Some were immediately frozen, cryosectioned and labelled for filamentous actin using phalloidin, and for the focal contact component vinculin or for vimentin by indirect immunofluorescence. Sections were examined by confocal microscopy and 3D modelling. Actin occurred in all chondrocytes, appearing as bright foci at the cell surface linked to an irregular network beneath the surface. Cell surface foci colocalised with vinculin, suggesting the presence of focal contacts between the chondrocyte and its pericellular matrix. Vimentin label occurred mainly in cells of the deep zone. It had a complex intracellular distribution, with linked networks of fibres surrounding the nucleus and beneath the plasma membrane. When cartilage explants were placed into organ culture, where in the absence of further treatments cartilage imbibes fluid from the culture medium and swells, cytoskeletal changes were observed. After 1 h in culture the vimentin cytoskeleton was disassembled, leading to diffuse labelling of cells. After a further hour in culture filamentous vimentin label reappeared in deep zone chondrocytes, and then over the next 48 h became more widespread in cells of the explants. Actin distribution was unaffected by culture. Further experiments were performed to test the effects of load on the cytoskeleton. Explants were placed in culture and immediately subjected to static uniaxial radially unconfined compressive loads of 0.5, 1, 2 or 4 MPa for 1 h using a pneumatic loading device. Loads greater than 0.5 MPa maintained the vimentin organisation over the culture period. At 0.5 MPa, the chondrocytes within the explant behaved as in free-swelling culture. The rapid change in vimentin organisation probably relates to rapid swelling of the explants--under free-swelling conditions, these reached their maximum swollen size in just 15 min of culture. The chondrocytes' response to change in tissue dimensions, and thus to their relationship to their immediate environment, was to disassemble their vimentin networks. Loading probably counteracts the swelling pressure of the tissue. Overall, this work suggests that chondrocytes maintain their actin cytoskeleton and modify their vimentin cytoskeleton in response to changing mechanical conditions.

11. Fragonas E, Valente M, Pozzi-Mucelli M, Toffanin R, Rizzo R, Silvestri F, Vittur F. Dipartimento di Biochimica, Biofisica e Chimica delle Macromolecole, Universita di Trieste, Italy. **Articular cartilage repair in rabbits by using suspensions of allogenic chondrocytes in alginate.** *Biomaterials*. 21(8):795-801, 2000 Apr.

Abstract

The feasibility of allogenic implants of chondrocytes in alginate gels was tested for the reconstruction in vivo of artificially full-thickness-damaged articular rabbit cartilage. The suspensions of chondrocytes in alginate were gelled by the addition of calcium chloride solution directly into the defects giving in situ a construct perfectly inserted and adherent to the subchondral bone and to the walls of intact cartilage. The tissue repair was controlled at 1, 2, 4 and 6 months after the implant by NMR microscopy, synchrotron radiation induced X-ray emission to map the sulfur of glycosaminoglycans and by histochemistry. Practically a complete repair of the defect was observed 4-6 months from the implant of the chondrocytes with the recovery of a normal tissue structure. Controls in which Ca-alginate alone was implanted developed only a fibrous cartilage.

12. Frenkel SR, Di Cesare PE. Musculoskeletal Research Center, Department of Orthopedic Surgery, New York University-Hospital for Joint Diseases, 301 E. 17 St., NY, NY 10003, USA. (Sally.frenkel@med.nyu.edu) **Degradation and repair of articular cartilage**. [Review] [137 refs] *Frontiers in Bioscience*. 4:D671-85, 1999 Oct 15.

Abstract

Approximately 95,000 total knee replacements and 41,000 other surgical procedures to repair cartilaginous defects of the knee are performed annually in the United States (1). The response of normal articular cartilage to injury or arthritic degeneration is often a sub-optimal repair; the biochemical and mechanical properties of the new tissue differ from the native cartilage, resulting in inadequate or altered function. It is believed that the chondrocytes from the surrounding areas, although perhaps capable of some limited migration at the damaged site, are not able to proliferate and produce the macromolecules necessary to create an organized matrix characteristic of normal articular cartilage (2,3). Current therapeutic options for articular cartilage injuries and degeneration have resulted in repair tissue which may be hyaline-like, but does not approximate the durability and function of the

normal articular surface. Numerous studies have been performed to increase our understanding of the normal repair process of articular cartilage and its limitations, and to devise methods and materials to regenerate the joint surface. [References: 137]

13. Frenkel SR, Toolan B, Menche D, Pitman MI, Pachence JM. Hospital for Joint Diseases, New York, NY 10003, USA. **Chondrocyte transplantation using a collagen bilayer matrix for cartilage repair** [see comments]. Comments Comment in: J Bone Joint Surg Br 1998 Jul;80(4):743-4. *Journal of Bone & Joint Surgery - British Volume*. 79(5):831-6, 1997 Sep.

Abstract

We have developed a novel, two-layered, collagen matrix seeded with chondrocytes for repair of articular cartilage. It consists of a dense collagen layer which is in contact with bone and a porous matrix to support the seeded chondrocytes. The matrices were implanted in rabbit femoral trochleas for up to 24 weeks. The control groups received either a matrix without cells or no implant. The best histological repair was seen with cell-seeded implants. The permeability and glycosaminoglycan content of both implant groups were nearly normal, but were significantly less in tissue from empty defects. The type-II collagen content of the seeded implants was normal. For unseeded implants it was 74.3% of the normal and for empty defects only 20%. The current treatments for articular injury often result in a fibrous repair which deteriorates with time. This bilayer implant allowed sustained hyaline-like repair of articular defects during the entire six-month period of observation.

14. Gerstenfeld LC, Toma CD, Schaffer JL, Landis WJ. Musculoskeletal Research Laboratory, Boston University Medical Center, Massachusetts 02118, USA. **Chondrogenic potential of skeletal cell populations: selective growth of chondrocytes and their morphogenesis and development in vitro**. *Microscopy Research & Technique*. 43(2):156-73, 1998 Oct 15.

Abstract

Most vertebrate embryonic and post-embryonic skeletal tissue formation occurs through the endochondral process in which cartilage serves a transitory role as the anlage for the bone structure. The differentiation of chondrocytes during this process in vivo is characterized by progressive morphological changes associated with the hypertrophy of these cells and is defined by biochemical changes that result in the mineralization of the extracellular matrix. The mechanisms, which, like those in vivo, promote both chondrogenesis in presumptive skeletal cell populations and endochondral progression of chondrogenic cells, may be examined in vitro. The work presented here describes mechanisms by which cells within presumptive skeletal cell populations become restricted to a chondrogenic lineage as studied within cell populations derived from 12-day-old chicken embryo calvarial tissue. It is found that a major factor associated with selection of chondrogenic cells is the elimination of growth within serum-containing medium. Chondrogenesis within these cell populations appears to be the result of permissive conditions which select for chondrogenic proliferation over osteogenic cell proliferation. Data suggest that chondrocyte cultures produce autocrine factors that promote their own survival or proliferation. The conditions for promoting cell growth, hypertrophy, and extracellular matrix mineralization of embryonic chicken chondrocytes in vitro include ascorbic acid supplementation and the presence of an organic phosphate source. The differentiation of hypertrophic chondrocytes in vitro is associated with a 10-15-fold increase in alkaline phosphatase enzyme activity and deposition of mineral within the extracellular matrix. Temporal studies of the biochemical changes coincident with development of hypertrophy in vitro demonstrate that proteoglycan synthesis decreases 4-fold whereas type X collagen synthesis increases 10-fold within the same period. Ultrastructural examination reveals cellular and extracellular morphology similar to that of hypertrophic cells in vivo with chondrocytes embedded in a well formed extracellular matrix of randomly distributed collagen fibrils and proteoglycan. Mineral deposition is seen in the interterritorial regions of the matrix between the cells and is apatitic in nature. These characteristics of chondrogenic growth and development are very similar in vivo and in vitro and they suggest that studies of chondrogenesis in vitro may provide a valuable model for the process in vivo.

15. Gilbert JE. Dept of Orthopedic Surgery, Baylor University Medical Ctr, Dallas, TX 75246, USA. **Current treatment options for the restoration of articular cartilage**. [Review] [12 refs]. *American Journal of Knee Surgery*. 11(1):42-6, 1998 Winter.

Abstract

Over the past several decades, much has been learned about articular cartilage and its physiological capacity to restore itself. While articular cartilage does appear to have some regenerative capabilities, it appears to lose this capacity over a period of time, making restoration of articular surfaces more and more difficult. To date, no technique has been completely successful in achieving exactly normal regenerative articular cartilage. Arthroscopic lavage and debridement provides temporary relief of symptoms. This probably works by removing degradative enzymes that contribute to synovitis and also to the further breakdown of articular cartilage. Bone marrow stimulation techniques such as abrasion arthroplasty, drilling, and microfracture produce only fibrocartilage and therefore do not offer a long-term cure. Perichondral and periosteal interposition grafts produce repair tissue that is similar to hyaline cartilage but also lack the mechanical durability. Like bone marrow stimulation techniques, interposition grafts introduce precursor cells, which have a tendency to differentiate along lines other than cartilage. This leads to an inferior

quality of repair tissue. Currently, chondrogenic-stimulating factors and artificial matrices are currently being researched and developed. Much has been learned about the various growth factors that stimulate chondrocyte differentiation and extracellular matrix production, but to date, there has not been a clinical technique that has shown any long-term promise. Ultimately, the goal will be to take precursor cells from an easily accessible source such as the iliac crest, mix them with growth factors that have been derived genetically in the lab, and provide an artificial matrix that in combination can produce restoration of articular cartilage at minimal cost and patient morbidity. Autologous osteochondral transplant systems have shown encouraging results but there are still problems. Graft matching and contouring to the recipient articular surface is difficult. Donor sites can be a limiting factor. Furthermore, the fibrocartilaginous interface between the donor and recipient site may contribute to breakdown in the long run. Autologous chondrocyte implantation is a biological repair process that also has shown encouraging results. It must be remembered that this is not normal articular cartilage--it is only hyaline-like cartilage. The technique is expensive and is technically difficult to perform. There are no randomized prospective studies that compare the natural history of the repair tissue to that of other forms of repair tissue. Long-term functional outcome is still a significant question mark. In addition, it has not been shown that autologous chondrocyte implantation can prevent degenerative changes. In the future, we probably will see delivery systems using stimulating growth factors, chondrocytes, and synthetically derived matrices. When placed in combination and with the right mechanical stimuli, we may ultimately achieve true restoration of articular cartilage. [References: 12]

16. Gillogly SD, Voight M, Blackburn T. Atlanta Knee and Shoulder Clinic, Georgia Baptist Orthopaedic Residency Program 30327, USA. **Treatment of articular cartilage defects of the knee with autologous chondrocyte implantation**. [Review] [64 refs] *Journal of Orthopaedic & Sports Physical Therapy*. 28(4):241-51, 1998 Oct.

Abstract

The treatment of focal full thickness articular defects in the knee has continued to present a challenge, with no traditional treatment method providing consistent acceptable long-term clinical results. Patients with significant chondral defects frequently have persistent joint line pain, swelling, and catching in the knee. In contrast to marrow stimulation treatment techniques, such as abrasion arthroplasty, drilling, or microfracture which populate the defect with pluripotential stem cells, the use of cultured autologous chondrocytes fills the defect with cells of a committed pathway to develop hyaline-like cartilage. This hyaline-like cartilage more closely recreates the wear characteristics and durability of normal hyaline cartilage than the fibrous or fibrocartilage repair tissue formed by pluripotential stem cells. The purpose of this paper is to review the efficacy of available treatment options as well as the basic science rationale, indications, technique, postoperative rehabilitation, and clinical results of using cultured autologous chondrocytes in the treatment of focal full thickness chondral defects of the knee. [References: 64]

17. Grande DA, Breitbart AS, Mason J, Paulino C, Laser J, Schwartz RE. Department of Surgery, North Shore Long Island Jewish Health System, Manhasset NY, USA. **Cartilage tissue engineering: current limitations and solutions**. *Clinical Orthopaedics & Related Research*. (367 Suppl):S176-85, 1999 Oct.

Abstract

Articular cartilage repair remains one of the most intensely studied orthopaedic topics. To date the field of tissue engineering has ushered in new methodologies for the treatment of cartilage defects. The authors' 10-year experience using principles of tissue engineering applied to resurfacing of cartilage defects is reported. Which cell type to use, chondrocytes versus chondroprogenitor cells, and their inherent advantages and disadvantages are discussed. Chondrocytes initially were used as the preferred cell type but were shown to have long term disadvantages in models used by the authors. Mesenchymal stem cells can be used effectively to overcome the limitations experienced with the use of differentiated chondrocytes. The use of mesenchymal stem cells as platforms for retroviral transduction of genes useful in cartilage repair introduces the concept of gene modified tissue engineering. The fundamental conditions for promoting and conducting a viable cartilage repair tissue, regardless of which cell type is used, also were studied. Placement of a synthetic porous biodegradable polymer scaffold was found to be a requirement for achieving an organized repair capable of functionally resurfacing a cartilage defect. A new modular device for intraarticular fixation of various graft composites has been developed. This new cartilage repair device is composed of bioabsorbable polymers and is capable of being delivered by the arthroscope.

18. Grandolfo M, Calabrese A, D'Andrea P. Dipartimento di Biochimica, Biofisica e Chimica delle Macromolecole, Universita di Trieste, Italy. **Mechanism of mechanically induced intercellular calcium waves in rabbit articular chondrocytes and in HIG-82 synovial cells**. *Journal of Bone & Mineral Research*. 13(3):443-53, 1998 Mar.

Abstract

Intercellular communication through gap junctions allows tissue coordination of cell metabolism and sensitivity to extracellular stimuli. Intercellular Ca2+ signaling was investigated with digital fluorescence video imaging in primary cultures of articular chondrocytes and in HIG-82 synovial cells. In both cell types, mechanical stimulation of a single cell induced a wave of increased Ca2+ that was communicated to surrounding cells. Intercellular Ca2+ spreading was inhibited by 18alpha-glycyrrhetinic acid, demonstrating the involvement of gap junctions in signal propagation. In the absence of extracellular Ca2+, mechanical

stimulation induced communicated Ca2+ waves similar to controls; however, the number of HIG-82 cells recruited decreased significantly. Mechanical stress induced Ca2+ influx both in the stimulated chondrocyte and HIG-82 cell, but not in the adjacent cells, as assessed by the Mn2+ quenching technique. Treatment of cells with thapsigargin and with the phospholipase C (PLC) inhibitor U73122 blocked mechanically induced signal propagation. These results provide evidence that in chondrocytes and in HIG-82 synovial cells, mechanical stimulation activates PLC, thus leading to an increase of intracellular inositol 1,4,5-trisphosphate. The second messenger, by permeating gap junctions, stimulates intracellular Ca2+ release in neighboring cells. It is concluded that intercellular Ca2+ waves may provide a mechanism to coordinate tissue responses in joint physiology.

19. Guilak F, Jones WR, Ting-Beall HP, Lee GM. Department of Surgery, Duke University Medical Center, Durham, NC 27710, USA. (guilak@duke.edu) **The deformation behavior and mechanical properties of chondrocytes in articular cartilage.** [Review] [58 refs] *Osteoarthritis & Cartilage*. 7(1):59-70, 1999 Jan.

Abstract

INTRODUCTION: Chondrocytes in articular cartilage utilize mechanical signals to regulate their metabolic activity. A fundamental step in determining the role of various biophysical factors in this process is to characterize the local mechanical environment of the chondrocyte under physiological loading. METHODS: A combined experimental and theoretical approach was used to quantify the in-situ mechanical environment of the chondrocyte. The mechanical properties of enzymatically-isolated chondrocytes and their pericellular matrix (PCM) were determined using micropipette aspiration. The values were used in a finite element model of the chondron (the chondrocyte and its PCM) within articular cartilage to predict the stress-strain and fluid flow microenvironment of the cell. The theoretical predictions were validated using three-dimensional confocal microscopy of chondrocyte deformation in situ. RESULTS: Chondrocytes were found to behave as a viscoelastic solid material with a Young's modulus of approximately 0.6 kPa. The elastic modulus of the PCM was significantly higher than that of the chondrocyte, but several orders of magnitude lower than that of the extracellular matrix. Theoretical modeling of cell-matrix interactions suggests the mechanical environment of the chondrocyte is highly non-uniform and is dependent on the viscoelastic properties of the PCM. Excellent agreement was observed between the theoretical predictions and the direct measurements of chondrocyte deformation, but only if the model incorporated the PCM. CONCLUSIONS: These findings imply that the PCM plays a functional biomechanical role in articular cartilage, and alterations in PCM properties with aging or disease will significantly affect the biophysical environment of the chondrocyte. [References: 58]

20. Hashimoto S, Ochs RL, Komiya S, Lotz M. The Scripps Research Institute, La Jolla, California 92037, USA. **Linkage of chondrocyte apoptosis and cartilage degradation in human osteoarthritis**. *Arthritis & Rheumatism*. 41(9):1632-8, 1998 Sep.

Abstract

OBJECTIVE: To examine the occurrence of apoptosis in human osteoarthritis (OA) cartilage, and to determine its relationship to cartilage degradation. METHODS: Knee cartilage was obtained from subjects at autopsy, from a tissue bank, and from OA patients undergoing total joint replacement surgery. Chondrocytes were isolated and the number of apoptotic cells was analyzed by flow cytometry. Apoptotic cells in cartilage sections were identified by the detection of DNA strand breaks. Electron microscopy was applied to demonstrate morphologic changes, and Safranin O staining was performed to analyze the relationship between apoptosis and proteoglycan depletion. RESULTS: Flow cytometry on cell suspensions prepared from collagenase digests of cartilage showed that approximately 22.3% of OA chondrocytes and 4.8% of normal chondrocytes were undergoing apoptosis. Staining of cartilage sections demonstrated the presence of apoptotic cells in the superficial and middle zones. Cartilage areas that contained apoptotic cells showed proteoglycan depletion, and the number of apoptotic cells was significantly correlated with the OA grade. CONCLUSION: These observations demonstrate increased chondrocyte apoptosis in OA cartilage. Chondrocyte apoptosis and proteoglycan depletion are anatomically linked and may be mechanistically related.

21. Hauselmann HJ, Flura T, Marti C, Hauser N, Hedbom E. Zentrum fur experimentelle Rheumatologie, Gruppe Matrix-Biologie, Rheumaklinik und Institut fur Physikalische Medizin, Universitatsspital Zurich. **[From chondrocyte culture to joint cartilage replacement. Development of de novo cartilage in vitro]. [Review] [31refs]** [German] *Schweizerische Medizinische Wochenschrift. Journal Suisse de Medecine*. 128(21):824-32, 1998 May 23.

Abstract

Local repair of acute or chronic cartilage lesions has not been successful so far. An attempt has been made to use synthetic materials to improve the quality of the repair tissue, but no method has achieved reliable regrowth of normal hyaline cartilage with adequate biomechanical properties and bonding to surrounding tissue. After publication of the first short-term results of chondrocyte transplantation in patients with localized cartilage lesions of the knee joints by a Swedish group in 1994 [1], the situation seems to have changed. Even though the advantages of this method of chondrocyte transplantation is a matter of controversy, the interest in the so-called "Carticel" approach has grown steadily. Indeed, the technique was recently approved by the FDA, on condition of a randomized, "placebo"-controlled trial. In view of this rapid development, we feel that independent

experimental studies are urgently needed. In this article we present our own results in synthesizing de novo cartilage from cultured and phenotypically stable chondrocytes in a truly three-dimensional cartilage-like polyanionic matrix. With the experience gained in animals, we expect to set the stage for future experimental therapy in young human patients with early cartilage lesions. [References: 31]

22. Hershler C, Sjaus A. **Pulsed Signal Therapy: Treatment of chronic pain due to traumatic soft tissue injury**. *International Medical Journal.* 1999;6(3).

Abstract

Introduction: Pulsed Signal Therapy (PST) is a form of therapy that involves directing a series of magnetic pulses through injured tissue. Each magnetic pulse induces a tiny electrical signal that stimulates cellular repair. PST has been used in the treatment of chronic pain associated with connective (bone, cartilage, tendon) tissue injury. A review of the current literature indicates that PST has a positive effect on bone and cartilage repair and leads to a decrease in chronic pain in patients with osteoarthritis. We examined the effect of PST in the treatment of joint associated soft tissue injury (traumatic, including motor vehicle accident).

Objective: We conducted a retrospective study to establish the effectiveness of pulsed electromagnetic fields (PST) in the treatment of chronic pain. We divided the PST patients into two groups:

1) Osteoarthritis (OA) Group N=45

This was a group of patients who were complaining of pain either in the spine or in a specific joint (knee, hip, ankle, shoulder). There was clearly documented evidence of OA with minimal soft tissue involvement.

2) Soft Tissue Injury (STI) Group N=35

This was a group of patients who were complaining of pain either in the spine or in a specific joint (knee/hip/shoulder) where no documented evidence of OA or bony change existed, but there was clinical evidence of soft tissue injury.

Data was extracted from standard PST evaluation forms which included the medical histories and diagnoses of all PST patients. This data was used as criteria for inclusion or exclusion of the subjects in the above two groups. The basis for the PST treatment's effectiveness was self reported symptom evaluations involving a five point visual analog scale (for pain intensity and frequency). This information was routinely obtained prior to the initial treatment, at the time of the final PST treatment (approximately 9 days later) and at a 6 week follow-up.

Results: Using a matched pair t-test, significant changes from base-line scores were found *within* both groups. By change we mean a decline in the intensity and/or frequency of pain. The differences between pre- and post-treatment scores were highly significant at the 6 week follow-up (in both groups $p<0.001$ for both clinical variables). The extent of the improvement was also compared *between* the groups. A modified X^2 (median) test showed no statistically significant difference between the means of these improvements in the two groups at the 6 week follow-up ($p>0.1$).

Conclusions:

1) The extent of improvement (after PST) at the six week follow-up for patients with joint-associated soft tissue injury is in the same range as improvement experienced by patients with OA.

2) Both groups of patients experience a statistically significant improvement (compared to their pre-treatment state) at six week post PST treatment.

This was not a controlled study and was based on data collected by the nurse/therapist on PST patients passing through the PST treatment protocol. All of the patients treated were complaining of chronic pain that had not responded to conventional therapy. The etiology of the pain was different in the two groups: the OA group included predominantly non-traumatic bony OA, while the cause of the pain in the soft tissue injury group was presumably trauma.

23. Honda M, Yada T, Ueda M, Kimata K. Department of Oral Surgery, Nagoya University School of Medicine, Japan (mahonda@med.nagoya-u.ac.jp). **Cartilage formation by cultured chondrocytes in a new scaffold made of poly(L-lactide-epsilon-caprolactone) sponge.** *Journal of Oral & Maxillofacial Surgery.* 58(7):767-75, 2000 Jul.

Abstract

PURPOSE: This study investigated the ability of chondrocytes grown in culture and inoculated into a newly developed biodegradable sponge to form ectopic cartilage tissue. MATERIALS AND METHODS: Chondrocytes obtained from costochondral cartilage dissected from Lewis rats were cultured to allow proliferation and then were inoculated into a sponge consisting of a biodegradable polymer, poly (L-lactide-epsilon-caprolactone). The composites of chondrocytes and sponge were transplanted subcutaneously into Nude mice and removed after 4 weeks for histologic and Northern blot analysis. RESULTS: Staining with hematoxylin and eosin showed the formation of a cartilage-like structure in the sponge. Northern blot analysis of the total RNA in the composites showed the presence of aggrecan transcripts of about 9 kb. CONCLUSION: The poly (L-lactide-epsilon-caprolactone) sponge system, is suitable as a matrix for tissue-engineered cartilage.

24. Huang MH, Ding HJ, Chai CY, Huang YF, Yang RC. Department of Rehabilitation Medicine, Kaohsiung Medical College Hospital, Taiwan. **Effects of sonication on articular cartilage in experimental osteoarthritis.** *Journal of Rheumatology*. 24(10):1978-84, 1997 Oct.

Abstract

OBJECTIVE: To investigate the histological effect of therapeutic ultrasound on arthritic cartilage of rats with various severities of induced osteoarthritis. METHODS: Twenty-seven rats with 3 different stages (Grade I, II, III) of papain induced knee arthritis received 7 min pulse sonication treatment, 3 times/week for 4 weeks. Another 27 rats with the same severity of induced arthritis were studied as controls. The severity of arthritis and related histopathological changes of articular cartilage were evaluated by bone scan and histological findings with hematoxylin and eosin stain. RESULTS: "Severity indexes" based on bone scan decreased after sonication treatment in each study group. Histopathological findings indicated marked cartilage repair in the early stage of induced arthritis (Grade I). However, progressive cartilage damage present in untreated Grade II, III induced arthritis was significantly reduced after sonication. CONCLUSION: Therapeutic ultrasound enhances cartilage repair in the early stage, and has the effect of arresting further deteriorative damage in the later stage of induced arthritis.

25. Hunziker EB. M. E. Muller-Institute for Biomechanics, University of Bern, Switzerland. (hunziker@mem.unibe.ch) **Articular cartilage repair: are the intrinsic biological constraints undermining this process insuperable?.** [Review] [103 refs] *Osteoarthritis & Cartilage*. 7(1):15-28, 1999 Jan.

Abstract

This article reviews the experimental and clinical strategies currently in use or under development for the treatment of articular cartilage lesions. The vast majority of protocols under investigation pertain to the treatment of full-thickness defects (i.e., those which penetrate the subchondral bone and trabecular-bone spaces) rather than partial-thickness ones (i.e., those which are confined to the substance of articular cartilage tissue itself). This bias probably reflects the circumstance that partial-thickness defects do not heal spontaneously whereas full-thickness ones below a critical size do, albeit transiently. And it is, of course, a seemingly easier task to manipulate a process which is readily set in train than it is to overcome an induction-problem which Nature herself has not solved. Indeed, the reasons for this inert state of partial-thickness defects have only recently been elucidated, and these are briefly discussed. However, the main body of this review deals with the various transplantation concepts implemented for the repair of full-thickness defects. These fall into two broad categories: tissue-based (entailing the grafting of perichondrial, periosteal, cartilage or bone-cartilage material) and cell-based (utilizing chondroblasts, chondrocytes, periochondrial cells or mesenchymal stem cells). Cell-based systems are further subdivided according to whether cells are transplanted within a matrix (biodegradable, non-biodegradable or synthetic) or free in suspension. Thus far, the application of cell suspensions has always been combined with the grafting of a periosteal flap. The strengths and weaknesses of each concept are discussed. [References: 103]

26. Katsube K. Ochi M. Uchio Y. Maniwa S. Matsusaki M. Tobita M. Iwasa J. Department of Orthopaedics, Shimane Medical University, Izumo-shi, Shimane-ken, Japan. (katsube@shimane-med.ac.jp). **Repair of articular cartilage defects with cultured chondrocytes in Atelocollagen gel. Comparison with cultured chondrocytes in suspension.** *Archives of Orthopaedic & Trauma Surgery.* 120(3-4):121-7, 2000.

Abstract

We attempted to repair full-thickness articular cartilage defects in rabbit knee joints with allogeneic cultured chondrocytes embedded in Atelocollagen gel. An articular cartilage defect was created on the patellar groove of the femur. The defect was filled with chondrocytes cultured in the collagen gel and covered with periosteal flap (G group). In three other experimental groups, the same defects were transplanted with chondrocytes in monolayer culture with periosteal flap (M group), periosteal graft only (P group), or left empty (E group). At 4, 12, and 24 weeks after operation, the reparative tissue was analyzed macroscopically and histologically. At 4 weeks after operation, the surfaces of the reparative tissue were smooth, and the defects were filled with reparative tissues that resembled hyaline cartilage in all four groups. However, the reparative tissues degenerated gradually with time in the M, P, and E groups. In contrast, in the G group, the reparative tissue retained its thickness, and there was a steady integration of the grafted tissue into the adjacent normal cartilage at 24 weeks after operation. The results suggest that transplantation of allogeneic chondrocytes cultured in Atelocollagen gel is effective in repairing an articular cartilage defect.

27. Kawamura S, Wakitani S, Kimura T, Maeda A, Caplan AI, Shino K, Ochi T. Department of Orthopedics, Osaka University Medical School, Japan. **Articular cartilage repair. Rabbit experiments with a collagen gel-biomatrix and chondrocytes cultured in it.** *Acta Orthopaedica Scandinavica*. 69(1):56-62, 1998 Feb.

Abstract

To repair a full-thickness articular cartilage defect in rabbit knees, we developed a technique of using a collagen gel hardened by cultured allogeneic chondrocytes in it. The gel-chondrocyte composite accumulated an intense metachromatic matrix, and had

elasticity and stiffness enough to be shaped easily after 2 weeks' culture in vitro. It was implanted into full-thickness articular cartilage defects. Histologic evaluation was performed up to 6 months after surgery, using a histologic grading scale composed of 5 categories. In the gel-chondrocyte composite implanted group, good repair was observed from as early as 1 day up to 6 months. On the other hand, in the empty control group, no repair was observed 1 day to 2 weeks after the defects were made. At 4 weeks, some repair occurred, but even at 6 months the repair was not good.

28. Knutsen G, Solheim E, Johansen O. Ortopedisk avdeling Regionsykehuset i Tromso. **[Treatment of focal cartilage injuries in the knee]**. [Review] [31 refs] [Norwegian] *Tidsskrift for Den Norske Laegeforening*. 118(16):2493-7, 1998 Jun 20.

Abstract

Chondrocytes in adult human cartilage have little mitotic capacity even after injuries. Deep injuries penetrating the subchondral bone plate lead to the release of pluripotent mesenchymal stem cells which have the potential to differentiate into different types of connective tissue, including bone and cartilage. The release and stimulation of these stem cells can also be achieved by drilling or microfracture of the subchondral bone of cartilage lesions. When stimulated, periosteal cells may also differentiate into chondrocytes. However, non-chondrocyte determined cells seem to induce mainly fibrocartilage. In 1987 autologous chondrocyte implantation was introduced by a team in Gothenburg. This resulted in clinical improvement and the development of hyaline-like cartilage in patients who had undergone treatment. We first used the method in 1996 in a clinical trial. At a 6-month follow-up of our first 12 patients we found reduced symptoms and improved knee function. This method is promising, but further clinical trials are necessary. [References: 31]

29. Lee MC, Sung KL, Kurtis MS, Akeson WH, Sah RL. Department of Orthopedic Surgery, Seoul National University College of Medicine, Korea. **Adhesive force of chondrocytes to cartilage. Effects of chondroitinase ABC.** *Clinical Orthopaedics & Related Research*. (370):286-94, 2000 Jan.

Abstract

Chondrocyte transplantation is a clinical procedure for cartilage repair. Transplanted cells may have difficulty attaching to the surface of chondral lesions because of the anti-adhesive properties of the proteoglycan rich matrix. This study used micromanipulation methods to determine if pretreatment of cartilage with chondroitinase ABC affects chondrocyte adhesion to cartilage and if chondrocytes adhere preferentially to the superficial, middle, or deep layers of cartilage. Bovine chondrocytes were transplanted in vitro on articular cartilage sections cut perpendicular to the articular surface. At various times between 15 and 75 minutes after seeding, a micropipette micromanipulation system was used to measure the adhesion force of individual chondrocytes to cartilage. The chondrocyte adhesion force increased with chondroitinase ABC treatment and seeding time but generally was similar for the different regions of articular cartilage (superficial, middle, deep layer) to which the cells were attached. For normal cartilage, the adhesion force increased from 1.29 +/- 0.24 mdyne after 15 to 30 minutes seeding to 5.29 +/- 0.25 mdyne after 60 to 75 minutes. Treatment with chondroitinase ABC at certain concentrations and durations (1.0 U/mL for 5 minutes or 0.5 or 1 U/mL for 15 minutes) led to an increase in adhesion force, whereas relatively low concentration or treatment time (0.25 U/mL for 15 minutes or 0.5 U/mL for 5 minutes) had little or no detectable effect. The increase in adhesion attributable to chondroitinase ABC treatment appeared most marked (+144% to +292%) for short (15 to 30 minutes) seeding durations but was still significant (+46%) for the longest seeding period (60 to 75 minutes) studied after the 1 U/mL for 15 minute treatment condition. These results provide direct biomechanical evidence that enzymatic treatment of a cartilage surface can enhance chondrocyte adhesion.

30. Lohnert J. Chirurgische Abteilung, St. Marien-Hospital, Gelsenkirchen-Buer. **[Regeneration of hyalin cartilage in the knee joint by treatment with autologous chondrocyte transplants--initial clinical results].** [German] *Langenbecks Archiv fur Chirurgie - Supplement - Kongressband*. 115:1205-7, 1998.

Abstract

Treatment with autologous chondrocyte transplantation (ACT) leads to regeneration of hyaline cartilage. Since September 1996, 52 patients have been treated. Eleven patients were screened clinically and by MRI 18 months later. The biopsy specimen from the transplanted area showed formation of hyaline cartilage.

31. Minas T. Department of Orthopedics, Brigham and Women's Hospital, Boston, Massachusetts, USA. **Chondrocyte implantation in the repair of chondral lesions of the knee: economics and quality of life** [see comments]. Comment in: Am J Orthop 1999 Jun;28(6):374. *American Journal of Orthopedics* (Chatham, NJ). 27(11):739-44, 1998 Nov.

Abstract

Autologous chondrocyte implantation (ACI) has proven clinically effective in restoring hyaline-like cartilage to isolated chondral defects of the knee. This study prospectively examined the efficacy of treatment and quality of life in 44 patients undergoing ACI

for full-thickness cartilage lesions and calculated the average cost per additional quality-adjusted life year. The 12-month results of ACI treatment showed improvement in patient function as measured by both the Knee Society score (114.02 to 140.67, or a 23% mean improvement, P < .001) and the Western Ontario and McMaster Universities Osteoarthritis Index (35.30 to 23.82, or a 33% mean improvement, P < .05). Quality of life, as measured by the Short Form-36 Physical Component Summary, was dramatically enhanced from 33.32 prior to biopsy to 41.48 (P < .05) 12 months after implantation. Improvement on all three scales was maintained during the period from 12 to 24 months after surgery. The estimated cost per additional quality-adjusted life year was $6791. This cost-effectiveness ratio was minimally sensitive to reasonable changes in effectiveness, patient age, or procedure cost. The procedure remained cost effective even when assumptions were less favorable than those in the base case. ACI improves patient quality of life, and it is an appropriate, cost-effective treatment for cartilage lesions of the knee.

32. Morrone G, Guzzardella GA, Tigani D, Torricelli P, Fini M, Giardino R. Department of Experimental Surgery, Rizzoli Orthopaedic Institute Bologna, Italy. **Biostimulation of human chondrocytes with Ga-Al-As diode laser: 'in vitro' research.** *Artificial Cells, Blood Substitutes, & Immobilization Biotechnology*. 28(2):193-201, 2000 Mar.
Abstract:
The aim of this study was to verify the effects of laser therapy performed with Ga-Al-As Diode Lasers (780 nm, 2500 mW) on human cartilage cells in vitro. The cartilage sample used for the biostimulation treatment was taken from the right knee of a 19-year-old patient. After the chondrocytes were isolated and suspended for cultivation, the cultures were incubated for 10 days. The cultures were divided into four groups. Groups I, II, III were subject to biostimulation with the following laser parameters: 300 J, 1 W, 100 Hz, 10 min. exposure, pulsating emission; 300 J, 1 W, 300 Hz, 10 min. exposure, pulsating emission; and 300 J, 1 W, 500 Hz, 10 min. exposure, pulsating emission, respectively. Group IV did not receive any treatment. The laser biostimulation was conducted for five consecutive days. At the end of the treatment, the Calcium, Alkaline Phosphate, MTT tests and proteoglycan were performed to assess cell metabolism and toxicity level. The data showed good results in terms of cell viability and levels of Ca and Alkaline Phosphate in the groups treated with laser biostimulation compared to the untreated group. The results obtained confirm our previous positive in vitro results that the Ga-Al-As Laser provides biostimulation without cell damage.

33. Papacrhistou G, Anagnostou S, Katsorhis T. Department of Orthopaedics, University of Athens Medical School, Greece. **The effect of intraarticular hydrocortisone injection on the articular cartilage of rabbits.** *Acta Orthopaedica Scandinavica. Supplementum*. 275:132-4, 1997 Oct.
Abstract
We investigated the effect of hydrocortisone on the articular cartilage of the knee in rabbits. 27 New Zealand white rabbits were injected intraarticularly with 25, 50 or 100 mg betamethasone acetate in 2 or 4 weekly intervals. Control animals were injected with normal saline and demonstrated no histological changes in the articular cartilage. Hydrocortisone administration was associated with increased cell size, as well as an increased stain density in the cytoplasm surrounding vacuoles. In addition, loss of cell organelles was also observed. High dose of hydrocortisone was associated with an obvious loss of cell shape and distortion of the cell membrane and nucleus. The magnitude of histological changes, found under light and electron microscopy, were proportional to the amount of hydrocortisone injected. Our findings strongly indicate that intraarticular injection of hydrocortisone alters the shape of articular cartilage chondrocytes, producing abnormal changes in the cytoplasm and nucleus and leading to cell degeneration.

34. Perka C, Schultz O, Lindenhayn K, Spitzer RS, Muschik M. Sittinger M, Burmester GR. Department of Orthopedics, Charite University Hospital, Humboldt University of Berlin, Germany. **Joint cartilage repair with transplantation of embryonic chondrocytes embedded in collagen-fibrin matrices.** *Clinical & Experimental Rheumatology.* 18(1):13-22, 2000 Jan-Feb.
Abstract
OBJECTIVE: The objective of this study was to assess the feasibility of transplanting embryonic chondrogenic cells within a collagen-fibrin substrate for the reconstitution of full-thickness cartilage defects in chicken knee joints. METHODS: Full-thickness cartilage defects were created mechanically on the weight-bearing surface of the tibial condyle in 45 adult chickens and subsequently filled with chondrocytes embedded in a chondrocyte-collagen-fibrin gel. The transplants were compared to untreated defects and collagen-fibrin transplants without cells. The results were analyzed using histochemical and morphometrical methods after 3, 12 and 24 weeks. A semiquantitative histological grading system was applied to evaluate the transplant integration and the newly formed cartilage architecture. RESULTS: Chondrocyte-gel grafts developed to hyaline-like cartilage without any granulation tissue in the interface after 3 weeks. After 12 weeks the defects in the experimental group were filled completely with hyaline cartilage. The defects in the control groups in all cases healed with fibrous repair tissue. CONCLUSION: Fibrin-collagen gel allowed stable graft fixation and provided an adequate microenvironment for embryonic chondrocytes to generate hyaline-like neocartilage in a full-thickness cartilage defect.

35. Perka C, Spitzer RS, Lindenhayn K, Sittinger M, Schultz O. Department of Orthopedics, University-Hospital Charite, Berlin, Germany. (carsten.perka@charite.de). **Matrix-mixed culture: new methodology for chondrocyte culture and preparation of cartilage transplants.** *Journal of Biomedical Materials Research*. 49(3):305-11, 2000.

Abstract

For cartilage engineering a variety of biomaterials were applied for 3-dimensional chondrocyte embedding and transplantation. In order to find a suitable carrier for the in vitro culture of chondrocytes and the subsequent preparation of cartilage transplants we investigated the feasibility of a combination of the well-established matrices fibrin and alginate. In this work human articular chondrocytes were embedded and cultured either in alginate, a mixture of alginate and fibrin, or in a fibrin gel after the extraction of the alginate component (porous fibrin gel) over a period of 30 days. Histomorphological analysis, electron microscopy, and immunohistochemistry were performed to evaluate the phenotypic changes of the chondrocytes, as well as the quality of the newly formed cartilaginous matrix. Our experiments showed that a mixture of 0.6% alginate with 4.5% fibrin promoted sufficient chondrocyte proliferation and differentiation, resulting in the formation of a specific cartilage matrix. Alginate served as a temporary supportive matrix component during in vitro culture and can be easily removed prior to transplantation. The presented tissue engineering method on the basis of a mixed alginate-fibrin carrier offers the opportunity to create stable cartilage transplants for reconstructive surgery. Copyright 2000 John Wiley & Sons, Inc.

36. Peretti GM, Randolph MA, Caruso EM, Rossetti F, Zaleske DJ. Orthopaedic Department, San Raffaele Hospital, Milan, Italy. **Bonding of cartilage matrices with cultured chondrocytes: an experimental model**. *Journal of Orthopaedic Research*. 16(1):89-95, 1998 Jan.

Abstract

The capacity of isolated chondrocytes to join separate masses of cartilage matrix was investigated with composites implanted in subcutaneous pouches in nude mice. Slices of articular cartilage were harvested from lambs and were devitalized by cyclic freezing and thawing. The slices were then either co-cultured with viable allogeneic lamb chondrocytes (experimental) or cultured without such chondrocytes (control). Composites of three slices were constructed with use of fibrin glue and were implanted in nude mice for periods ranging from 7 to 42 days. Bonding of the experimental matrices with viable chondrocytes was achieved at 28 and 42 days, as assessed by direct examination, histology, thymidine uptake, and fluorescence. No bonding occurred in the control composites without viable chondrocytes. We conclude that devitalized cartilage matrix is a scaffold to which isolated chondrocytes can attach and begin to repopulate.

37. Peterson L, Minas T, Brittberg M, Nilsson A, Sjogren-Jansson E, Lindahl A. Sahlgrenska University Hospital, Goteborg, Sweden. **Two-to 9-year outcome after autologous chondrocyte transplantation of the knee.** *Clinical Orthopaedics & Related Research.* (374):212-34, 2000 May.

Abstract

Autologous cultured chondrocyte transplantation was introduced in Sweden in1987 for the treatment of large (1.5-12.0 cm2) full thickness chondral defects of the knee. The clinical, arthroscopic, and histologic results from the first 101 patients treated using this technique are reported in this study. Patients were assessed retrospectively using three types of endpoints: patient and physician derived clinical rating scales (five validated and two new); arthroscopic assessment of cartilage fill, ntegration, and surface hardness; and standard histochemical techniques. Ninety-four patients with 2- to 9-years followup were evaluable. Good to excellent clinical results were seen in individual groups as follows: isolated femoral condyle (92%), multiple lesions (67%), osteochondritis dissecans (89%), patella (65%), and femoral condyle with anterior cruciate ligament repair (75%). Arthroscopic findings in 53 evaluated patients showed good repair tissue fill, good adherence to underlying bone, seamless integration with adjacent cartilage, and hardness close to that of the adjacent tissue. Hypertrophic response of the periosteum or graft or both was identified in 26 arthroscopies; seven were symptomatic and resolved after arthroscopic trimming. Graft failure occurred in seven (four of the first 23 and three of the next 78) patients. Histologic analysis of 37 biopsy specimens showed a correlation between hyalinelike tissue (hyaline matrix staining positive for Type II collagen and lacking a fibrous component) and good to excellent clinical results. The good clinical outcomes of autologous chondrocyte transplantation in this study are encouraging, and clinical trials are being done to assess the outcomes versus traditional fibrocartilage repair techniques.

38. Pezzetti F, De Mattei M, Caruso A, Cadossi R, Zucchini P, Carinci F, Traina GC, Sollazzo V. Dipartimento di Morfologia ed Embriologia, Universita di Ferrara, via Fossato di Mortara 64, 44100 Ferrara, Italy. **Effects of pulsed electromagnetic fields on human chondrocytes: an in vitro study.** *Calcified Tissue International.* 65(5):396-401, 1999 Nov.

Abstract

(3)H-thymidine incorporation was studied in cultured human nasal and articular chondrocytes exposed to low-energy, low-frequency pulsed electromagnetic fields (PEMFs) (75 Hz, 2.3 mT). The reverse transcriptase polymerase chain reaction (RT-PCR) analysis shows that human secondary chondrocytes derived from both nasal and articular cartilage express collagen type II mRNA, which is a specific marker of the chondrocyte phenotype. In a preliminary series of experiments, cells were exposed to PEMF for different time periods ranging from 6 to 30 hours (time-course), in medium supplemented with 10% or 0.5% fetal calf serum (FCS) and in serum-free medium. The ratios between the (3)H-thymidine incorporation in PEMFs and control cultures show an increase of the cell proliferation in cultures exposed to PEMFs when serum is present in the culture medium, whereas no effect was observed in serum-free conditions. The increase in DNA synthesis, induced by PEMFs, was then evaluated only at the times of maximum induction and the results were analyzed by the three-factor analysis of variance (ANOVA). The data presented in this study show that even if (3)H-thymidine incorporation is higher in nasal than in articular chondrocytes, PEMF induce an increase in the proliferation of both cell types. Moreover, the concentration of FCS in the culture medium greatly influences the proliferative response of human chondrocytes to the PEMF exposure. Though normal human osteoblast cells increase their proliferation when exposed to PEMFs if only 10% FCS is present in the medium, human chondrocytes are able to increase their cell proliferation when exposed to PEMFs in the presence of both 0.5% and 10% of FCS in the medium. The results obtained may help to explain the basic mechanisms of PEMF stimulation of fracture healing.

39. Quinn TM, Grodzinsky AJ, Buschmann MD, Kim YJ, Hunziker EB. Department of Electrical Engineering and Computer Science, Massachusetts Institute of Technology, Cambridge, MA 02139, USA. **Mechanical compression alters proteoglycan deposition and matrix deformation around individual cells in cartilage explants**. *Journal of Cell Science*. 111 (Pt 5):573-83, 1998 Mar.

Abstract

We have used new techniques of cell-length scale quantitative autoradiography to assess matrix synthesis, deposition, and deformation around individual chondrocytes in mechanically compressed cartilage explants. Our objectives were to: (1) quantify the effects of static and dynamic compression on the deposition of newly synthesized proteoglycans into cell-associated and further-removed matrices; (2) measure cell-length scale matrix strains and morphological changes of the cell and matrix associated with tissue compression; and (3) relate microscopic physical stimuli to changes in proteoglycan synthesis as functions of compression level and position within mechanically compressed explants. Results indicate a high degree of structural organization in the extracellular matrix, with the pericellular matrix associated with the most rapid rates of proteoglycan deposition, and greatest sensitivity to mechanical compression. Static compression could stimulate directional deposition of secreted proteoglycans around chondrocytes, superimposed on an inhibition of proteoglycan synthesis; these events followed trends for compressive strain in the cell-associated matrix. Conversely, proteoglycan synthesis and pericellular deposition was stimulated by dynamic compression. Results suggest that cell-matrix interactions in the cell-associated matrix may be a particularly important aspect of the chondrocyte response to mechanical compression, possibly involving macromolecular transport limitations and morphological changes associated with fluid flow and local compaction of the matrix around cells.

40. Rahfoth B, Weisser J, Sternkopf F, Aigner T, von der Mark K, Brauer R. Clinicum Erfurt, Orthopaedic Clinic, F.R.G. **Transplantation of allograft chondrocytes embedded in agarose gel into cartilage defects of rabbits.** *Osteoarthritis & Cartilage*. 6(1):50-65, 1998 Jan.

Abstract

OBJECTIVE: Durable healing of full-thickness articular cartilage defects has been considered for a long time as a highly desirable, but unlikely event to occur. In recent years, conflicting reports on the outcome of in vitro and in vivo studies on chondrocyte and cartilage grafting into animal and human joints have raised new arguments for and against controlled repair of articular cartilage following injury. Some of the problems result from insufficient characterization of implant and repair tissue, and from too short follow up phases. Here we describe a new approach to repair articular cartilage defects in rabbit knees by allografting chondrocytes cultured in agarose gels. DESIGN: The implants were monitored over 6-18 months and graded histologically, munohistochemically, and electron microscopically, using a grading scale based on seven evaluation criteria. Control implants of pure agarose produced poor fibrous substitute tissue, insufficient healing and incomplete filling of the cartilage defects. After transplantation of allogenic chondrocytes embedded in agarose, the quality of the newly formed repair cartilage was superior with respect to type II collagen and proteoglycan content and cellular architecture when compared with untreated defects. Superficial fibrillation and degradation were significantly diminished or prevented. RESULTS: New subchondral bone formed at the level of the previous subchondral bone. In most cases the repair tissue merged with the host articular cartilage; normal calcified cartilage was the only tissue zone that did not participate in the integration of the transplant. By gross evaluation 24% of grafts showed an extent of recovery never observed in controls. The best results were obtained after 18 months when 47% of the grafts (N = 15) developed a morphologically stable hyaline cartilage. CONCLUSION: These studies demonstrate that agarose-embedded chondrocyte may prove a valuable tool for controlled repair of articular cartilage defects.

41. Riesle J, Hollander AP, Langer R, Freed LE, Vunjak-Novakovic G. Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge 02139, USA. **Collagen in tissue-engineered cartilage: types, structure, and crosslinks.** *Journal of Cellular Biochemistry*. 71(3):313-27, 1998 Dec 1.

Abstract

The function of articular cartilage as a weight-bearing tissue depends on the specific arrangement of collagen types II and IX into a three-dimensional organized collagen network that can balance the swelling pressure of the proteoglycan/water gel. To determine whether cartilage engineered in vitro contains a functional collagen network, chondrocyte-polymer constructs were cultured for up to 6 weeks and analyzed with respect to the composition and ultrastructure of collagen by using biochemical and immunochemical methods and scanning electron microscopy. Total collagen content and the concentration of pyridinium crosslinks were significantly (57% and 70%, respectively) lower in tissue-engineered cartilage that in bovine calf articular cartilage. However, the fractions of collagen types II, IX, and X and the collagen network organization, density, and fibril diameter in engineered cartilage were not significantly different from those in natural articular cartilage. The implications of these findings for the field of tissue engineering are that differentiated chondrocytes are capable of forming a complex structure of collagen matrix in vitro, producing a tissue similar to natural articular cartilage on an ultrastructural scale.

42. Richardson JB, Caterson B, Evans EH, Ashton BA, Roberts S. Robert Jones and Agnes Hunt Orthopaedic and District Hospital, Oswestry, England. **Repair of human articular cartilage after implantation of autologous chondrocytes.** *Journal of Bone & Joint Surgery - British Volume*. 81(6):1064-8, 1999 Nov.

Abstract

Tissue engineering is an increasingly popular method of addressing pathological disorders of cartilage. Recent studies have demonstrated its clinical efficacy, but there is little information on the structural organisation and biochemical composition of the repair tissue and its relation to the adjacent normal tissue. We therefore analysed by polarised light microscopy and immunohistochemistry biopsies of repair tissue which had been taken 12 months after implantation of autologous chondrocytes in two patients with defects of articular cartilage. Our findings showed zonal heterogeneity throughout the repair tissue. The deeper zone resembled hyaline-like articular cartilage whereas the upper zone was more fibrocartilaginous. The results indicate that within 12 months autologous chondrocyte implantation successfully produces replacement cartilage tissue, a major part of which resembles normal hyaline cartilage.

43. Robert H, Bahuaud J. HIA Rene Picque, Villeneuve D'Ornon. **Autologous chondrocyte implantation. A review of techniques and preliminary results.** [Review] [17 refs]. *Revue Du Rhumatisme*, English Edition. 66(12):724-7, 1999 Dec.

Abstract

The treatment of deep focal bone and cartilage defects in weight-bearing areas of the knee remains challenging. Autologous chondrocyte implantation is a recently introduced alternative to drilling and mosaicplasty and is gaining ground in France under the impetus of favorable results obtained in other countries in highly selected cases. The technique and preliminary results are discussed herein. [References: 17]

44. Rudert M, Hirschmann F, Wirth CJ. Orthopadische Klinik, Medizinische Hochschule Hannover. **[Growth behavior of chondrocytes on various biomaterials]. [German]** *Orthopade*. 28(1):68-75, 1999 Jan.

Abstract

Chondrocytes can be cultured on different three-dimensional culture systems suitable for transplantation to enhance the repair of localized cartilage defects. Articular cartilage chondrocytes from adult rabbit knees and from bovine calf metacarpophalangeal joints were isolated by enzymatic digestion and cultured in a monolayer system to amplify cell count. After amplification the cells were seeded on different biocompatible materials. We investigated two types of bioresorbable polymer fleece matrices (a composite fleece of polydioxanon and polyglactin and a resorbable poly-L-lactic acid fleece) and lyophilized dura as a biological carrier. On all three types of transport media the phenotypic and morphological appearance of cultured chondrocytes could be observed. The production of glycosaminoglycans was revealed by Alcian blue staining and immunohistochemical detection of Chondroitin-4 and 6-sulfate in the created constructs. The material properties of the carriers allow for transplantation of the artificial cartilage-like products into full thickness articular cartilage defects and could therefore improve the minor intrinsic healing capacity of cartilage tissue. Bioartificial cartilage may become a future perspective in the treatment options of orthopaedic and plastic surgery.

45. Schreiber RE, Ilten-Kirby BM, Dunkelman NS, Symons KT, Rekettye LM, Willoughby J, Ratcliffe A. Advanced Tissue Sciences, Inc., La Jolla, CA 92037-1005, USA. **Repair of osteochondral defects with allogeneic tissue engineered cartilage implants.** *Clinical Orthopaedics & Related Research*. (367 Suppl):S382-95, 1999 Oct.

Abstract

The objective of this study was to evaluate the effect of allogeneic tissue engineered cartilage implants on healing of osteochondral defects. Rabbit chondrocytes were cultured in monolayer, then seeded onto biodegradable, three-dimensional polyglycolic acid meshes. Cartilage constructs were cultured hydrodynamically to yield tissue with relatively more (mature) or less (immature) hyalinelike cartilage, as compared with adult rabbit articular cartilage. Osteochondral defects in the patellar grooves of both stifle joints either were left untreated or implanted with allogeneic tissue engineered cartilage. Histologic samples from in and around the defect sites were examined 3, 6, 9, and 12, and 24 months after surgery. By 9 months after surgery, defects sites treated with cartilage implants contained significantly greater amounts of hyalinelike cartilage with high levels of proteoglycan, and had a smooth, nonfibrillated articular surface as compared to untreated defects. In contrast, the repair tissue formed in untreated defects had fibrillated articular surfaces, significant amounts of fibrocartilage, and negligible proteoglycan. These differences between treated and untreated defects persisted through 24 months after surgery. The results of this study suggest that the treatment of osteochondral lesions with allogenic tissue engineered cartilage implants may lead to superior repair tissue than that found in untreated osteochondral lesions.

46. Sims CD, Butler PE, Cao YL, Casanova R, Randolph MA, Black A, Vacanti CA, Yaremchuk MJ. Department of Surgery, Harvard Medical School, and Massachusetts General Hospital, Boston 02114, USA. **Tissue engineered neocartilage using plasma derived polymer substrates and chondrocytes**. *Plastic & Reconstructive Surgery*. 101(6):1580-5, 1998 May.

Abstract

This study demonstrates that fibrin monomers can be polymerized into moldable gels and used for the encapsulation of isolated chondrocytes. This biologically derived scaffold will maintain three-dimensional spatial support, allowing new tissue development in a subcutaneous space. Chondrocytes isolated from the glenohumeral and humeroradioulnar joints of a calf were combined with cyroprecipitate and polymerized with bovine thrombin to create a fibrin glue gel with a final cell density of 12.5 x 10(6) cells/ml. The polymer-chondrocyte constructs were implanted subcutaneously in 12 nude mice and incubated for 6 and 12 weeks in vivo. Histologic and biochemical analysis including deoxyribonucleic acid (DNA) and glycosaminoglycan quantitation confirmed the presence of actively proliferating chondrocytes with production of a well-formed cartilaginous matrix in the transplanted samples. Control specimens from 12 implantation sites consisting of chondrocytes alone or fibrin glue substrates did not demonstrate any gross or histologic evidence of neocartilage formation. Moldable autogenous fibrin glue polymer systems have a potential to serve as alternatives to current proprietary polymer systems used for tissue engineering cartilage as well as autogenous grafts and alloplastic materials used for facial skeletal and soft-tissue augmentation.

47. Steinwachs MR, Erggelet C, Lahm A, Guhlke-Steinwachs U. Cartilage Research Group, Orthopadische Abteilung, Albert-Ludwigs-Universitat Freiburg. **[Clinical and cell biology aspects of autologous chondrocytes transplantation]**. [Review] [30 refs] [German] *Unfallchirurg*. 102(11):855-60, 1999 Nov.

Abstract

The treatment of deep cartilage defects is a challenge for every orthopaedic surgeon. The potential for regeneration of cartilage tissue is minimal and leads to mechanically inferior fibrous tissue. The established techniques induce the growth of fibrous tissue but fail to prevent arthrosis. Autologous chondrocyte transplantation seems to be the most promising therapy concept with clinical relevance to reserves a full thickness cartilage defect with hyaline-like cartilage. Outcome studies with a follow up from 2-10 years show in up to 90 % good and excellent results for defects on the femoral condyle and 70 % for the patella. Mechanical testing of the regenerated cartilage showed almost similar stiffness as nearly normal hyaline cartilage. The available data justify the acceptance of autologous chondrocyte transplantation as a standard procedure for limited indications and well-trained surgeons. Result of already inaugurated studies will show the potential of chondrocyte transplantation to prevent osteoarthritis. [References: 30]

48. Ting V, Sims CD, Brecht LE, McCarthy JG, Kasabian AK, Connelly PR, Elisseeff J, Gittes GK, Longaker MT. Department of Surgery and the Institute of Reconstructive Surgery, New York University Medical Center, New York 10016, USA. **In vitro prefabrication of human cartilage shapes using fibrin glue and human chondrocytes.** *Annals of Plastic Surgery.* 40(4):413-20; discussion 420-1, 1998 Apr.

Abstract

We report the first generation of human cartilage from fibrin glue using a technique of molding chondrocytes in fibrin glue developed in our laboratory. Human costal chondrocytes were suspended in cryoprecipitate and polymerized into a human nasal shape with bovine thrombin. After culture in vitro for 4 weeks, this construct was implanted subcutaneously into a nude mouse. The final construct harvested after 4 weeks in vivo demonstrated some preservation of its original features. Histological analysis showed features of native cartilage, including matrix synthesis and viable chondrocytes by nuclear staining. Biochemical analysis demonstrated active matrix production. Biomechanical testing was performed. To our knowledge this is the first reported creation

of human cartilage from fibrin glue, and the first creation of human cartilage in vitro. This technique may become a promising means of engineering precisely designed autogenous cartilage for human reconstruction.

49. Wu JZ, Herzog W, Epstein M. Faculty of Kinesiology, Department of Mechanical Engineering, University of Calgary, Alberta, Canada. **Modelling of location- and time-dependent deformation of chondrocytes during cartilage loading.** *Journal of Biomechanics*. 32(6):563-72, 1999 Jun.

Abstract

Experimental evidence suggests that the biosynthetic activity of chondrocytes is regulated primarily by the mechanical environment. In order to study the mechanisms underlying remodeling, adaptation, and degeneration of articular cartilage in a joint subjected to changing loads, it is important to know the time-dependent fluid pressure and stress-strain state in chondrocytes. The purpose of the present study was to develop a theoretical model to simulate the mechanical behaviour of articular cartilage and to describe the time-dependent stress-strain state and fluid pressure distribution in chondrocytes during cartilage deformation. It was assumed that the volume occupied by the chondrocytes is small and that cartilage can be treated as a macroscopically homogenized material with effective material properties which depend on the material properties of the cells and matrix and the volumetric fraction of the cells. Model predictions on the time-dependent distribution of fluid pressure and stress and on the time-dependent cell deformation during confined and unconfined compression tests agree with previous theoretical predictions and experimental observations. The proposed model supplies the tools to study the mechanisms of degeneration, adaptation and remodelling of cartilage associated with cell loading and deformation.

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