Title: Factors predictive of outcome five years following matrix-induced autologous chondrocyte implantation in the tibiofemoral joint.

Running Title: Factors predictive of outcome following MACI.

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TITLE

Factors predictive of outcome five years following matrix-induced autologous chondrocyte implantation in the tibiofemoral joint.

ABSTRACT

Background: Matrix-induced autologous chondrocyte implantation (MACI) has become an established technique for the repair of full thickness chondral defects in the knee. However, little is known about what variables most contribute to post-operative clinical and graft outcome, as well as overall patient satisfaction with the surgery.

Purpose: The aims of this study were to estimate the improvement in clinical and radiological outcome, and investigate the independent contribution of pertinent pre- and post-operative patient, chondral defect, injury/surgery history and rehabilitation factors to clinical and radiological outcome, as well as patient satisfaction, at five years following MACI.

Study Design: Cross-sectional study

Methods: This study was undertaken in 104 patients, out of an eligible 115 patients recruited, with complete clinical and radiological follow up at five years, following MACI surgery to the femoral or tibial condyles. Following a review of the literature, a range of pre- and post-operative variables that had demonstrated association with post-operative clinical and graft outcome were selected for investigation. These included age, gender and BMI, pre-operative SF-36 mental (MCS) and physical (PCS) scores, chondral defect size and location, DOS and prior surgeries, and post-operative time to full weight bearing gait. The 'Sport/Rec' and 'QOL' subscales of the KOOS were used as the patient-reported clinical evaluation tools at five years, while high resolution magnetic resonance imaging (MRI) was used to evaluate graft assessment. An MRI composite score was calculated based on the magnetic resonance observation of cartilage repair tissue (MOCART). A patient satisfaction questionnaire was completed by all patients at five years. Regression analysis was used to investigate the contribution of these pertinent variables to 5-year post-operative clinical, radiological and patient satisfaction outcomes.

Results: Pre-operative MCS, PCS and the duration of symptoms contributed significantly to the KOOS Sport/Rec score at five years while no variables, apart from baseline KOOS QOL score, contributed significantly to the KOOS QOL score at five years. Pre-operative MCS, duration of symptoms and graft size were statistically significant predictors of MRI score at five years post-surgery. An 8-week post-operative return to full weight bearing (versus 12 weeks) was the only variable significantly associated with an improved level of patient satisfaction at five years.

Conclusion: This study outlined factors such as pre-operative SF-36 scores, duration of knee symptoms, graft size and post-operative course of weight bearing rehabilitation as pertinent variables involved in 5-year clinical and radiological outcome, and overall satisfaction. This information may allow orthopaedic surgeons to better screen their patients as good candidates for MACI, while allowing treating therapists to better individualize their pre-operative preparatory and post-operative rehabilitation regimes for best possible outcome.

Keywords: matrix-induced autologous chondrocyte implantation, post-operative assessment, predictive variables.

What is known about this subject: Matrix-induced autologous chondrocyte implantation (MACI) has demonstrated good clinical efficacy for the repair of full thickness articular cartilage defects in the knee. However, little is known about what factors most contribute to post-operative clinical and graft outcome, as well as overall patient satisfaction with the MACI surgery. This is an area that requires investigation, and would allow orthopaedic surgeons to better screen their patients as good candidates for MACI, while allowing treating therapists to better individualize their post-operative rehabilitation regimes to every patient for the best possible outcome.

What this study adds to existing knowledge: A range of variables have been associated with patient and graft outcome following MACI, however, to what degree remains to be determined. Evaluating the contribution of these pertinent variables to both patient clinical and radiological outcome would provide benefits to orthopaedic surgeons and treating physical therapists alike. These data would provide a more accurate screening tool for surgeons to better assess which patients are deemed good candidates for MACI and who may have a better chance of successful clinical and graft outcome. It would also provide physical therapists working in the pre-operative preparation and post-operative rehabilitation of these patients with structured goals to enable better individual surgical outcome.

INTRODUCTION

Autologous chondrocyte implantation (ACI) is a cartilage restoration procedure that involves isolating and culturing a patient's own chondrocytes *in vitro*, and then re-implanting those cells into the cartilage defect. The first generation of the technique suspended these chondrocytes within the defect, sealing them with a periosteal cover.[8] While significant improvement in patient outcome has been reported using this method,[8, 43, 50, 51, 59, 60] a number of technical challenges and issues relating to the hypertrophic growth of the periosteal patch[47, 48] brought about the use of a biodegradable collagen membrane to contain the implanted chondrocytes, rather than periosteum. This second generation ACI method has also provided good clinical results,[1, 3, 27] though still failed to remove problems associated with suturing the cover such as the surgical complexity involved, the extensive micro-trauma that results, and cell leakage. Matrix-induced ACI (MACI)[4, 6, 20, 24] has provided the third and current generation of ACI, and does not use a periosteal or collagen patch. Instead, chondrocytes are seeded directly onto a synthetic membrane that can subsequently be cut to the exact size of the defect and fixed in place with fibrin glue, which has been shown to support migration and proliferation of human chondrocytes.[26, 37] This third generation has also permitted the development of arthroscopic surgical approaches,[10, 15, 21, 23, 44, 45, 57, 66] decreasing the associated co-morbidity of arthrotomy.[21] Over time, chondrocytes can differentiate into a durable load bearing tissue.

Several factors have been proposed to influence patient outcome and quality of repair tissue following ACI, including; 1) successful cell culturing, 2) efficiency of the surgical procedure, 3) patient cooperation in all aspects of the pre- and post-operative program, and 4) timely progression of weight bearing (WB) and post-operative rehabilitation. However, a range of other patient, injury, surgery and post-operative specific variables have also been associated with patient and graft outcome following MACI, though the relative importance of each of these to outcomes following MACI to the tibiofemoral joint remains unknown.

With respect to patient specific variables, age has been associated with both clinical[11, 38, 40] and graft[16, 17] outcomes following ACI, as has body mass index (BMI).[16, 34] Chondral defect size has exhibited a significant negative correlation with clinical outcome and pertinent parameters of morphological graft repair following ACI in the knee,[16, 17] though the association between defect location and aetiology on patient outcome remains less clear. The pre-operative duration of symptoms (DOS)[40, 62, 71] and number of knee surgeries[40] preceding ACI have also demonstrated an association with patient outcome. Finally, several papers have outlined the critical importance of structured post-operative rehabilitation following ACI for graft protection, facilitation of chondrocyte differentiation and development, and the return of the patient to normal physical function.[12, 28, 30, 32, 63, 64] Furthermore, the gradient and time to attain full WB post-surgery also appears to have an influence on clinical and functional outcomes following MACI to the WB femoral condyles.[17-19]

At present, the independent contribution of influential pre- and post-operative factors to post-operative MACI outcome is unknown. The aims of this study were to estimate the improvement in clinical and radiological outcome, and investigate the contribution of pertinent pre-operative patient demographics (age, gender and BMI) and general health (SF-36) parameters, chondral defect (size and location) and injury/surgery history (DOS, the number of prior knee surgeries and whether or not concomitant surgeries were performed at the time of surgery) variables, as well as early modifiable post-operative variables (post-operative time to full weight bearing), to clinical and radiological outcome, and patient satisfaction, at five years following MACI.

MATERIALS AND METHODS

Patients

Between August 2001 and June 2006, 115 MACI patients were recruited as part of two separate trials undertaken within our institution.[17, 20] This retrospective analysis was undertaken in 104 of those patients (62 males, 42 females) with complete clinical and radiological follow-up pre-surgery and at five years (+/- 2 months) post-surgery. All patients had undergone MACI to address localized, full thickness medial or lateral femoral or tibial condylar defects (73 medial femoral; 27 lateral femoral; 1 medial tibial; 3 lateral tibial) to the knee. Patients were 13-65 years of age and all underwent a structured rehabilitation program. Patients were excluded if they had a BMI > 35, had undergone a prior extensive meniscectomy or had ongoing progressive inflammatory arthritis. Patients with ligamentous instability or varus/valgus abnormalities (> 3° tibiofemoral anatomic angle) were included, provided these were addressed prior to or at the time of MACI grafting.

As per our routine clinical and research protocol, all patients had been screened pre-operatively for clinical knee joint instability by an orthopaedic specialist, and all patients underwent magnetic resonance imaging (MRI) to assess the location, size and severity of the chondral defect (if any) as well as any other soft tissue damage incorporating the menisci or ligamentous structures. All patients had suffered from persistent pain associated with grade III or IV chondral lesions, assessed pre-operatively with the International Cartilage Repair Society (ICRS) chondral defect classification system.[9] Of the 104 patients included in this retrospective follow-up, 77 (74.0%) had been previously treated with one or more surgical procedures to address knee pain and/or symptoms. These included arthroscopy (n, 60, not including the chondral biopsy required for cell culturing), microfracture (n, 7), partial meniscectomy (n, 19), anterior cruciate ligament (ACL) reconstruction (n, 9), extensor realignment (n, 3), lateral release (n, 9), and others (n, 8).

The mean age of patients was 38.0 years (range, 13-65 years), and the mean BMI was 26.7 (range, 16.8-33.3). At the time of surgery, 14 of the 104 knees had concomitant documented procedures at the time of MACI grafting, including high tibial osteotomy (n, 2), tibial tubercle transfer (n, 2), partial meniscectomy (n, 1), anterior cruciate ligament (ACL) reconstruction (n, 6), posterior cruciate ligament (PCL) reconstruction (n, 4) and lateral release (n, 1). A summary of the total patient cohort is provided in Table 1. Ethics approval for the recruitment and prospective follow-up of all patients was obtained from the relevant Human Research Ethics Committee.

Insert Table 1.

The MACI Surgical Technique

Over the duration of this research program, 10 orthopaedic surgeons had referred patients to our institution that subsequently fit the inclusion criteria and were recruited into the aforementioned trials.[20, 23] Therefore, while the MACI technique has been previously described,[20, 23] minor differences in surgical technique may exist between specialists. Briefly, MACI is a 2-stage technique, where arthroscopic surgery was performed to harvest a sample of articular cartilage from a non WB area of the knee. After harvest, chondrocytes were isolated, cultured and seeded onto a type I/III collagen membrane (ACI-Maix, Matricel GmbH, Herzogenrath, Germany) ex vivo over a 6- to 8-week period. At the time of second-stage implantation, the chondral defect was prepared via an open mini-arthrotomy by removing all damaged cartilage down to, but not through, subchondral bone. The resultant defect was measured and used to shape the membrane, which was secured to the bone using a thin layer of fibrin glue. The wound was closed after assessment of graft stability.

Outcome Measures

Knee Specific Patient Reported Outcome (PRO) Measure

All patients in this cohort completed the Knee Injury and Osteoarthritis Outcome Score (KOOS) at five years post-surgery, a knee specific questionnaire which includes 42 questions in five individual subscales: Pain, Symptoms, Activities of Daily Living (ADL), Sport and Recreation (Sport/Rec) and Knee Related Quality of Life (QOL).[69] Each of these five subscales is scored from 0 (worst) to 100 (best). The 'Sport/Rec' and 'QOL' subscales of the KOOS were used as the patient-reported clinical evaluation tools at five years for this retrospective analysis, as these scores were found to be most responsive to change after surgery (effect sizes of 1.64 and 1.37 respectively). The KOOS has been recommended for use with cartilage repair patients[67] and, more recently, has demonstrated validity and reliability in patients after the surgical treatment of focal cartilage lesions.[7] It has been used extensively in patients following ACI. [5, 15, 17, 20, 39, 55, 61, 65, 71, 76, 78]

Radiological Assessment

MACI grafts were assessed at five years post-surgery in all 104 patients using high resolution MRI. All MRI scans were performed using a Siemens Symphony 1.5 T scanner (Siemens, Erlangen, Germany). Standardized proton density and T2-weighted fat-saturated images were obtained in coronal and sagittal planes (slice thickness 3 mm, field of view 14-15 cm, 512 matrix in at least one axis for proton density images with a minimum 256 matrix in one axis for T2-weighted images). Additional axial proton density fat-saturated images were obtained (slice thickness 3-4 mm, field of view 14-15 cm, minimum 224 matrix in at least one axis).

MRI graft evaluation has been outlined previously.[13, 15, 18] Firstly, MRI parameters (signal intensity, graft infill, border integration, surface contour, structure, subchondral lamina, subchondral bone and effusion) were selected to best describe the morphology and signal intensity of the repair tissue, each scored individually from 1-4 (1=poor; 2=fair; 3=good; 4=excellent) in comparison to the native cartilage. An additional score of 3.5 for 'graft infill' was awarded for a fifth level (very good) corresponding with 'graft hypertrophy'.[47, 74] An MRI composite score was then calculated by multiplying each individual score by a weighting factor,[65] and summing the weighted scores.[16] This composite score also ranged from 1-4 (1=poor; 2=fair; 3=good; 4=excellent), and was used as our 5-year MRI-based outcome. MRI evaluation was performed by an independent, experienced musculoskeletal radiologist.

Patient Satisfaction

A patient satisfaction questionnaire was completed by all patients at five years post-surgery to investigate each patient's level of satisfaction with the MACI surgery overall, as well as their satisfaction with MACI in relieving knee pain, improving the ability to perform normal daily activities and their ability to participate in sport. These variables were scored with values ranging from 0-100 (0 = very dissatisfied; 100 = very satisfied).

Predictor Variables

Following a review of the literature, a range of pre- and post-operative factors that had previously demonstrated association with post-operative clinical and graft outcome were selected for investigation as follows.

Patient Demographics

Patient age,[11, 16, 17, 38, 40] gender and BMI[16] at the time of surgery were investigated.

Pre-operative General Health

The 36 item Short Form Health Survey (SF-36)[77] was completed by all 104 patients at five years post-surgery. It evaluates the general health of the patient and includes 36 questions spanning eight health domains: physical functioning, role limitations due to physical health problems, role limitations due to emotional problems, social functioning, vitality, mental health, bodily pain and general health perceptions. From these domains it produces a mental (MCS) and physical (PCS) component score, whereby the domains within each score are summed, weighted, and transformed to fall between 0 (worst possible health, severe disability) and 100 (best possible health, no disability).[56, 77]

Defect Characteristics

Chondral defect characteristics at the time of surgery including defect size[16, 17] and location[11] (medial or lateral condyle: 73 medial femoral; 27 lateral femoral; 1 medial tibial; 3 lateral tibial) were investigated.

Patient Injury and Surgery History

The DOS,[16, 40, 62, 71] the number of prior knee surgeries[40] on the affected knee and whether or not concomitant surgeries were performed at the time of MACI grafting, were investigated.

Post-operative Time to Full Weight Bearing

This retrospective analysis was made possible by two separate research trials. In brief, the first trial consisted of a patient cohort that underwent a structured rehabilitation program with a return to full WB at 12 weeks post-surgery.[20] The second trial involved a rehabilitation program identical in content, though these patients were randomly allocated to an 8- or 12-week progressive return to full WB.[17] Therefore, the time taken to reach full WB (8 or 12 weeks) was investigated in this analysis.

Statistical Analysis

Paired t-tests were used to estimate the degree of change in outcomes from pre-surgery to five years post-surgery. Pearson's correlation coefficient (or Spearman's rho in the case of Satisfaction scores) was used to quantify the association between outcome measures.

Linear regression analysis (ANCOVA) was used to evaluate predictors of clinical and radiological outcomes, conditioning on baseline scores in the case of the clinical outcomes. Tobit regression analysis with bootstrapped confidence intervals was used for the analysis of Satisfaction scores, as the distribution of this variable was left-skewed with 29 of 104 (27.9%) observations censored at the upper bound of 100 (very satisfied). For each regression model, potential predictors were first evaluated univariably, and those displaying associations with outcomes at $p<0.100$ were included in a multivariable regression model for the particular outcome. The final step was a purposeful selection of covariates by removing non-significant variables from the initial multivariable model one at a time whilst ensuring remaining coefficients did not change more than 20% to ensure retention of important confounders in the model, as recommended by Hosmer et al.[33] Models were evaluated for linearity of effects, homogeneity of variance of residuals and absence of influential outliers by examination of added variable plots and standard regression diagnostics.

RESULTS

Descriptive statistics of baseline clinical scores, surgical parameters and 5-year outcome variables are presented in Table 1.

KOOS Sport/Rec

The 5-year post-operative KOOS Sport/Rec score was 63.1±27.1 points (Table 1). The mean improvement from pre-surgery was 39.2 points (95% CI: 33.9 to 44.6, $p<0.001$), and 91 of 104 (87.5%) patients had an improvement greater than or equal to 10 points. The 5-year post-operative KOOS Sport/Rec score was moderately and significantly correlated with the 5-year post-operative KOOS QOL score ($r=0.664$, $p<0.001$) and Satisfaction score ($r=0.585$, $p<0.001$), but not with the MRI composite score ($r=0.015$, $p=0.900$).

Table 2 displays the results of univariable and multivariable linear regression models with the 5-year post-operative KOOS Sport/Rec score as the outcome variable. MCS, PCS and the DOS contributed significantly to a final multivariable model adjusting for the baseline Sport/Rec score. A 1-point increase in the baseline Sport/Rec score was associated with a predicted increase of 0.33 points (95% CI: 0.12 to 0.55, $p=0.003$) in 5-year post-operative Sport/Rec score. A 1-point increase in MCS was estimated to predict a 0.52 point increase in the mean 5-year Sport/Rec score (95% CI: 0.04 to 0.99, $p=0.035$), while a 1-point increase in PCS was estimated to predict a 0.63 point increase (95% CI: 0.09 to 1.16, $p=0.022$). The mean 5-year Sport/Rec score was estimated to decrease by 0.67 points for each year of symptoms (95% CI: -0.05 to -1.29, $p=0.036$). The standardized betas (change in units of SD of MRI score for 1SD increase in predictor) were 0.296, 0.185, 0.222 and -0.185 respectively. The adjusted R^2 for this model was 0.246.

Insert Table 2.

KOOS QOL

The 5-year post-operative KOOS QOL score was 58.5±23.1 points (Table 1). The mean improvement from post-surgery was 29.2 points (95% CI: 24.4 to 34.0, $p<0.001$), and 83 of 104 (79.8%) patients had an improvement greater than or equal to 10 points. The 5-year post-operative KOOS QOL score was moderately and significantly correlated with 5-year post-operative Satisfaction score ($r=0.623$, $p<0.001$), but not with the MRI composite score ($r=-0.044$, $p=0.655$).

Table 3 displays the results of univariable and multivariable linear regression models with 5-year post-operative KOOS QOL score as the outcome variable. No variable other than baseline QOL score contributed significantly to the linear regression model. A 1-point increase in baseline QOL score was associated with a predicted increase of 0.41 points (95% CI: 0.21 to 0.60, $p<0.001$) in 5-year post-operative score, corresponding to a standardized beta of 0.384. The adjusted R^2 of this model was 0.134.

Insert Table 3.

MRI Composite Score

The 5-year MRI composite score was 3.0±0.7 points (Table 1), and was not significantly correlated with the Satisfaction score (r=.017, p=o.864). Table 4 displays the results of univariable and multivariable linear regression models with the MRI Composite Score at five years as the outcome variable. Pre-operative factors univariably associated with a higher 5-year MRI score were younger age, shorter DOS, fewer previous knee procedures and a smaller graft size. In the final multivariable model baseline MCS, DOS and graft size were statistically significant predictors of MRI score. A 1-point increase in the baseline MCS was estimated to predict a 0.01 point increase (95% CI: 0.00 to 0.03, p=0.036) in mean MRI composite score. Each year of DOS was estimated to decrease the mean MRI composite score by 0.03 (95% CI: -0.01 to -0.04, p=0.002), while an increase in defect size of 1cm^2 was associated with a decrease in the MRI composite score of 0.08 (95% CI :-0.14 to -0.03, p=0.003). The standardized betas (change in units of SD of MRI score for 1SD increase in predictor) were 0.194, -0.292 and -0.276, respectively. The adjusted R^2 for this model was 0.134.

Insert Table 4.

Satisfaction Score

The 5-year Satisfaction scores ranged from 0 to 100, with a mean of 76.2±25.6 and a median of 83.3 (IQR: 36.7). Baseline MCS and 8-week (versus 12-week) time to FWB were univariably associated with a better 5-year satisfaction score (Table 5). The final tobit model retained only time to FWB, where a 12-week time versus an 8-week time to FWB was associated with a decrease in the mean Satisfaction score of 14.9 (95% CI: 1.7 to 28.0 points, p=0.027), corresponding to a standardized beta of -0.225. The pseudo-R^2 (McKelvey & Zavoina's R^2) measure of this model was 0.076.

Insert Table 5.

DISCUSSION

While MACI has demonstrated good clinical efficacy for the repair of full thickness articular cartilage defects in the knee,[4, 6, 20, 24] we understand little about the contribution of known influential pre- and post-operative factors to post-operative outcome. Patients significantly improved from pre-surgery to five years post-surgery in the KOOS Sport/Rec and QOL subscales, whereby 87.5% (Sport/Rec) and 79.8% (QOL) of patients had an improvement greater than 10 points. While the MCID for the KOOS has not been assessed for patients undergoing cartilage repair or ACI, a MCID of 8-10 points has been suggested in patients following ACL reconstruction.[68] No variables contributed significantly to the KOOS QOL score at five years, in addition to the baseline KOOS QOL score. However, in addition to the baseline KOOS Sport/Rec score, pre-operative SF-36 (MCS and PCS) scores and DOS contributed significantly to the KOOS Sport/Rec score at five years. Bartlett et al.[2] have previously demonstrated that higher pre-operative SF-36 scores are associated with better post-operative clinical outcome following ACI, suggesting that the SF-36 may prove beneficial in both the pre-operative assessment and post-operative review of ACI patients.[2]

A shorter DOS has been associated with improved post-operative clinical outcome following ACI[40, 62, 71] and morphological graft repair as assessed by MRI.[16] It is thought that a short (acute injury) history of trauma, pain and symptoms leading up to the MACI procedure are decisive factors in a good clinical outcome, when compared with long-standing trauma or patients suffering from degenerative cartilage defects.[62] This may also relate to 'defect age', whereby long-standing lesions may experience advanced degeneration of surrounding bone and cartilage, providing a possible adverse intra-articular environment.[70] Furthermore, inferior clinical results have also been observed in patients who have undergone three or more knee surgeries preceding ACI.[40]

With respect to the MRI-based outcomes, factors univariably associated with a higher 5-year MRI score were younger age, pre-operative MCS, shorter DOS, fewer previous knee procedures and a smaller graft size, though this was restricted to pre-operative MCS, DOS and graft size in the final statistical model. The potential relevance of a better pre-operative SF-36 score (MCS and/or PCS), a shorter DOS and fewer previous knee surgeries has been already discussed. However, chondral defect size has previously exhibited a significant negative correlation with clinical outcome and pertinent parameters of morphological graft repair following ACI in the knee, as assessed by MRI at two[16] and five[17] years post-surgery. Recent research has suggested that an upper limit of 7.5 cm^2 may exist in which, after this level, a poorer graft outcome may be observed.[17] However, contradictory results in the knee have been reported.[11, 52, 78]

Patient age has shown a significant negative correlation with clinical outcome[11, 38, 40] following ACI, as well as pertinent parameters of morphological graft repair as assessed by MRI at two[16] and five[17] years post-surgery.[13, 25, 42] Age restrictions are generally indicated for ACI surgery[36, 58] since, as one ages, there is an associated reduction in tissue regenerative capacity. However, while age was univariably associated with MRI-based outcome in this retrospective analysis, it did not significantly contribute to 5-year clinical or MRI-based outcomes in the final multivariable model. Analysis suggested that a substantial degree of the association between age and MRI outcome was explained by defect size and DOS.

The only factor that significantly contributed to patient satisfaction in the final multivariable model was an 8-week post-operative return to full WB (versus 12 weeks). Several papers have outlined the importance of post-operative rehabilitation following ACI and,[12, 28, 30, 32, 63, 64] while programs differ between institutions, a graded program incorporating progressive exercise and partial WB is recommended.[18, 28] We have previously demonstrated that the gradient and time to attain full WB post-surgery does influence clinical and functional patient outcome following MACI to the WB condyles.[17-19] Interestingly, despite the association with satisfaction, the faster return to full WB demonstrated no significant association on either five year clinical or MRI-based outcomes in this analysis. Satisfaction draws on the patient's memory of their pre-operative state, the surgical procedure and the early, mid and later post-operative phases, as opposed to a PRO measure which simply involves comparison of one score with that reported at a different point in time. The reliability of patients' estimates of previous health status has been questioned, whereby the events intervening between the anchor points influence the recall of the original status,[31] such as the early post-operative course of rehabilitation.

Other predictive factors that did not contribute to 5-year outcomes in this analysis as anticipated, or had demonstrated an association with patient outcome following ACI in prior studies, included BMI, graft location, pre-operative activity level and other potentially deleterious lifestyle factors. Of importance to the tibial or femoral WB condyles, BMI has previously demonstrated a significant negative correlation with clinical[34] and MRI-based[16] outcome. Jaiswal et al.[34] recently demonstrated that obese patients have worse knee function pre-operatively and experience no sustained benefit at two years after ACI or MACI. It has been previously demonstrated that any reduction in body weight results in a four-fold reduction in loads experienced at the knee during normal ambulation and daily activities,[49] which in turn, may overload post-operative repair tissue. This does highlight the importance of pre-operative weight loss and post-operative weight maintenance. The correlation between BMI and patient outcome was not conveyed in this analysis, suggesting that either BMI is not as important in the longevity of a tibiofemoral MACI graft as we think; or any negative ramifications of excessive BMI on graft outcome have been skewed, since patients were screened for excessive BMI prior to surgery. Unfortunately, this retrospective analysis assessed a cohort in which only 20.2% (21/104) were classified as obese (BMI>30).

While prior research has demonstrated better clinical improvement with medial femoral condylar grafts in comparison to lateral,[11] we did not observe a significant association between either medial or lateral compartment grafts, with five year outcomes, in this analysis. In addition to graft size and location, cell quality at the time of implantation (collagen type II expression, CD44 expression and cell viability) has been correlated with improved post-operative outcome,[53] while the presence of severe subchondral bone marrow oedema deep to the chondral lesion prior to surgery has been associated with a poorer clinical outcome.[54] While this was not information documented in this analysis, this may suggest that pre-operative MRI assessment of bony oedema may provide an additional prognostic factor for the early clinical course after ACI. Finally, other co-morbidities or social habits have also demonstrated association with ACI outcome. Jaiswal et al.[35] demonstrated that both clinical and ACI graft outcome (failure rate) was associated with smoking; a strong negative correlation was observed between the amount of cigarettes smoked and post-operative outcome. This was not information documented or used in this analysis.

Interestingly, while the KOOS Sport/Rec and QOL subscale scores were significantly correlated at five years, and both were significantly correlated with the Satisfaction score, neither significantly correlated with the MRI composite score. This may reflect PRO measures that are not specific enough to detect changes and/or improvements resulting from ACI. Although the KOOS has been used routinely for ACI,[2, 18, 46, 55, 65] a recent report stated that there are currently no cartilage repair-specific outcome measures.[29] With the development of more specific tools to assess patients following ACI, a higher association between clinical and MRI-based results may emerge. Alternatively, these findings may just reflect the vast amount of external biopsychosocial influences on the patient's perception and behavioral response to pain through measured function, which will influence patient-reported scores. These findings do indicate that, at present, both MRI-based and clinical PRO measures are important, and combine to assess both patient and graft outcome. An important aim of ACI is to reduce pain and symptoms, whilst returning the patient to a normally active lifestyle; variables that can only be reported verbally (or through questionnaires) by the patient. However, the ability of ACI to produce a hyaline-like regenerative tissue that may withstand the high loading demands placed upon it, and prevent or delay the onset of osteoarthritis associated with articular cartilage pathology, can only be assessed by methods such as MRI.

A number of limitations existed within this research. Firstly, this study evaluates patient reported outcome and satisfaction, psychosocial constructs potentially influenced by many factors not considered in this study. Variables in the final models accounted for only a small amount of variability in KOOS outcomes, though still meaningful, with R^2 (0.246 and 0.134 for Sport/Rec and QOL, respectively) above the recommended minimum effect size representing a 'practical' effect for psychosocial outcomes.[22] Although not directly comparable, relatively little of the variance in satisfaction (pseudo-R^2 = 0.076) was explained by the predictors in this study. The R^2 value of 0.134 for the MRI score was fairly low for a biological measure and it is possible that factors not considered in this study may further explain variance in this outcome. These may include the health of the knee and patient at the time of surgery and throughout the post-operative timeline, cell quality at implantation and patient activity level. The frequency and intensity of physical activity/sport may provide valuable information as to its contribution to patient outcome and satisfaction.

Secondly, our sample size did permit analysis with respect to the medial or lateral condyles. However, the analysis was primarily on the femoral condyles, given the few tibial cases. Our goal was to evaluate the tibiofemoral joint, as opposed to the isolated femoral condyles, and excluding the four tibial grafts resulted in very similar statistical estimates. Nevertheless, a larger sample in the future may permit a more specific analysis with respect to the influence of these predictor variables on tibial MACI and, while we would expect femoral and tibial grafts to be affected similarly by these predictor variables, grafts on the anterior, mid and/or posterior femoral/tibial condyles are subjected to different loads and articulation profiles, and may be influenced by different variables. Furthermore, this analysis did not accommodate for a variety of different defect aetiologies which may play a role in final outcome.[62] Thirdly, the small size and heterogeneity of the subgroup of patients that had concomitant documented procedures at the time of MACI grafting precludes detection of the influence of particular concomitant procedures on outcome. It can only be concluded that as a group, with the numbers available, there was no evidence of a difference in any outcome between those patients with and without concomitant procedures. A larger sample of particular procedures is needed to confirm the absence of influence of concomitant procedures on outcome.

Fourthly, for the assessment of radiological outcome we employed a morphological MRI composite score.[46, 65, 74, 75] New methods of assessing the biochemical characteristics of repair tissue are emerging.[41, 72, 73] This may assist in evaluating the 'ultra-structure' of the repair tissue[14] and, in time, may reflect a more accurate assessment of MRI-based outcome, thereby altering the influence of these predictors on MRI-based outcome. Finally, we employed PROs for clinical assessment that we use routinely within our institution. As outlined by Hambly and Griva,[29] there is currently no agreement on a 'gold standard' patient-assessed measure for the evaluation of cartilage repair surgery, let alone ACI. Therefore, PRO measures specific to articular cartilage repair (and ACI) need to be developed for these studies.

This study outlined factors such as pre-operative SF-36 scores, duration of knee symptoms, graft size and post-operative course of weight bearing rehabilitation as pertinent variables involved in 5-year clinical and radiological outcome, and overall satisfaction. This analysis may provide a more accurate screening tool for surgeons to better assess which patients are deemed good candidates for MACI, and those with a better chance at a successful clinical and/or graft outcome. It also provides physical therapists working in the pre-operative preparation and post-operative rehabilitation of these patients structured goals to enable better individual surgical outcome. To our knowledge, there is no research investigating the contribution of patient, injury, surgery and post-operative variables to patient outcome following MACI. While time will provide a larger MACI patient cohort in which a more detailed analysis can be undertaken with respect to the influence of these predictor variables on specific graft aetiology and location (anterior, mid and/or posterior condyles), other areas of the knee can also be assessed (patellofemoral joint). Furthermore, a larger cohort will permit the inclusion of additional variables, such as those not provided in this analysis including differing surgical techniques (open or arthroscopic), patient activity level, cell quality at implantation, other lifestyle factors and general knee and subchondral bone health.

REFERENCES

1. Amin A, Bartlett W, Gooding CR, et al. The use of autologous chondrocyte implantation following and combined with anterior cruciate ligament reconstruction. *Int Orthop.* 2005:1-6.

2. Bartlett W, Gooding CR, Carrington RW, Briggs TW, Skinner JA, Bentley G. The role of the Short Form 36 Health Survey in autologous chondrocyte implantation. *The Knee.* 2005;12:281-285.

3. Bartlett W, Skinner JA, Gooding CR, et al. Autologous chondrocyte implantation versus matrix-induced autologous chondrocyte implantation for osteochondral defects of the knee: a prospective, randomised study. *J Bone Joint Surg Br.* 2005;87(5):640-645.

4. Basad E, Ishaque B, Bachmann G, Sturz H, Steinmeyer J. Matrix-induced autologous chondrocyte implantation versus microfracture in the treatment of cartilage defects of the knee: a 2-year randomised study. *Knee Surg Sports Traumatol Arthrosc.* 2010;18(4):519-527.

5. Bauer S, Khan RJ, Ebert JR, et al. Knee joint preservation with combined neutralising High Tibial Osteotomy (HTO) and Matrix-induced Autologous Chondrocyte Implantation (MACI) in younger patients with medial knee osteoarthritis: A case series with prospective clinical and MRI follow-up over 5years. *Knee.* 2011.

6. Behrens P, Bitter T, Kurz B, Russlies M. Matrix-associated autologous chondrocyte transplantation/implantation (MACT/MACI) - 5-year follow-up. *Knee.* 2006;13(3):194-202.

7. Bekkers JE, de Windt TS, Raijmakers NJ, Dhert WJ, Saris DB. Validation of the Knee Injury and Osteoarthritis Outcome Score (KOOS) for the treatment of focal cartilage lesions. *Osteoarthritis Cartilage.* 2009;17(11):1434-1439.

8. Brittberg M, Lindahl A, Nilsson A, Ohlsson C, Isaksson O, Peterson L. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. *N Engl J Med.* 1994;331(14):889-895.

9. Brittberg M, Winalski CS. Evaluation of cartilage injuries and repair. *J Bone Joint Surg Am.* 2003;85-A Suppl 2:58-69.

10. Carey-Smith R, Ebert JR, Davies H, Garrett S, Wood DJ, Janes GC. Arthroscopic Matrix-induced Autologous Chondrocyte Implantation (MACI): A Simple Surgical Technique. *Techniques in Knee Surgery.* 2010;9(3):170-175.

11. de Windt TS, Bekkers JE, Creemers LB, Dhert WJ, Saris DB. Patient profiling in cartilage regeneration: prognostic factors determining success of treatment for cartilage defects. *Am J Sports Med.* 2009;37 Suppl 1:58S-62S.

12. Deszczynski J, Slynarski K. Rehabilitation after cell transplantation for cartilage defects. *Transplant Proc.* 2006;38(1):314-315.

13. Dixon S, Harvey L, Baddour E, Janes G, Hardisty G. Functional outcome of matrix-associated autologous chondrocyte implantation in the ankle. *Foot & ankle international / American Orthopaedic Foot and Ankle Society [and] Swiss Foot and Ankle Society.* 2011;32(4):368-374.

14. Domayer SE, Welsch GH, Dorotka R, et al. MRI monitoring of cartilage repair in the knee: a review. *Semin Musculoskelet Radiol.* 2008;12(4):302-317.

15. Ebert JR, Fallon M, Ackland TR, Wood DJ, Janes GC. Arthroscopic Matrix-Induced Autologous Chondrocyte Implantation: 2-Year Outcomes. *Arthroscopy.* 2012.

16. Ebert JR, Fallon M, Robertson WB, et al. Radiological assessment of accelerated versus traditional approaches to post-operative rehabilitation following matrix-induced autologous chondrocyte implantation (MACI). *Cartilage.* 2011;2(1):60-72.

17. Ebert JR, Fallon M, Zheng MH, Wood DJ, Ackland TR. A Randomized Trial Comparing Accelerated and Traditional Approaches to Postoperative Weightbearing Rehabilitation After Matrix-Induced Autologous Chondrocyte Implantation: Findings at 5 Years. *Am J Sports Med.* 2012.

18. Ebert JR, Robertson WB, Lloyd DG, Zheng MH, Wood DJ, Ackland T. Traditional vs accelerated approaches to post-operative rehabilitation following matrix-induced autologous chondrocyte implantation (MACI): comparison of clinical, biomechanical and radiographic outcomes. *Osteoarthritis Cartilage.* 2008;16:1131-1140.

19. Ebert JR, Robertson WB, Lloyd DG, Zheng MH, Wood DJ, Ackland T. A Prospective, Randomized Comparison of Traditional and Accelerated Approaches to Postoperative Rehabilitation following Autologous Chondrocyte Implantation: 2-Year Clinical Outcomes. *Cartilage.* 2010;1(3):180-187.

20. Ebert JR, Robertson WB, Woodhouse J, et al. Clinical and magnetic resonance imaging-based outcomes to 5 years after matrix-induced autologous chondrocyte implantation to address articular cartilage defects in the knee. *Am J Sports Med.* 2011;39(4):753-763.

21. Erggelet C, Sittinger M, Lahm A. The arthroscopic implantation of autologous chondrocytes for the treatment of full-thickness cartilage defects of the knee joint. *Arthroscopy.* 2003;19(1):108-110.

22. Ferguson C. An effect size primer: a guide for clinicians 2 and researchers. *Prof Psychol: Res Pr.* 2009;40(5):532-538.

23. Ferruzzi A, Buda R, Faldini C, et al. Autologous chondrocyte implantation in the knee joint: open compared with arthroscopic technique. Comparison at a minimum follow-up of five years. *J Bone Joint Surg Am.* 2008;90 Suppl 4:90-101.

24. Genovese E, Ronga M, Angeretti MG, et al. Matrix-induced autologous chondrocyte implantation of the knee: mid-term and long-term follow-up by MR arthrography. *Skeletal Radiol.* 2010;40:47-56.

25. Giannini S, Buda R, Vannini F, Di Caprio F, Grigolo B. Arthroscopic Autologous Chondrocyte Implantation in Osteochondral Lesions of the Talus: Surgical Technique and Results. *Am J Sports Med.* 2008.

26. Gille J, Meisner U, Ehlers EM, Muller A, Russlies M, Behrens P. Migration pattern, morphology and viability of cells suspended in or sealed with fibrin glue: a histomorphologic study. *Tissue Cell.* 2005;37(5):339-348.

27. Gooding CR, Bartlett W, Bentley G, Skinner JA, Carrington R, Flanagan A. A prospective, randomised study comparing two techniques of autologous chondrocyte implantation for osteochondral defects in the knee: Periosteum covered versus type I/III collagen covered. *Knee.* 2006;13(3):203-210.

28. Hambly K, Bobic V, Wondrasch B, Van Assche D, Marlovits S. Autologous Chondrocyte Implantation Postoperative Care and Rehabilitation: Science and Practice. *Am J Sports Med.* 2006;34:1-19.

29. Hambly K, Griva K. IKDC or KOOS? Which measures symptoms and disabilities most important to postoperative articular cartilage repair patients? *Am J Sports Med.* 2008;36(9):1695-1704.

30. Hambly K, Silvers H, Steinwachs M. Rehabilitation after Articular Cartilage Repair of the Knee in the Football (Soccer) Player. *Cartilage.* 2012;3(Suppl. 1):50S-56S.

31. Herrmann D. Reporting current, past, and changed health status. What we know about distortion. *Med Care.* 1995;33(4 Suppl):AS89-94.

32. Hirschmuller A, Baur H, Braun S, Kreuz PC, Sudkamp NP, Niemeyer P. Rehabilitation After Autologous Chondrocyte Implantation for Isolated Cartilage Defects of the Knee. *Am J Sports Med.* 2011.

33. Hosmer D, Lemeshow S. *Applied logistic regression*. 2nd ed. New York: John Wiley & Sons; 2000.

34. Jaiswal PK, Bentley G, Carrington RW, Skinner JA, Briggs TW. The adverse effect of elevated body mass index on outcome after autologous chondrocyte implantation. *J Bone Joint Surg Br.* 2012;94(10):1377-1381.

35. Jaiswal PK, Macmull S, Bentley G, Carrington RW, Skinner JA, Briggs TW. Does smoking influence outcome after autologous chondrocyte implantation?: A case-controlled study. *J Bone Joint Surg Br.* 2009;91(12):1575-1578.

36. Jones DG, Peterson L. Autologous chondrocyte implantation. *J Bone Joint Surg Am.* 2006;88(11):2502-2520.

37. Kirilak Y, Pavlos NJ, Willers CR, et al. Fibrin sealant promotes migration and proliferation of human articular chondrocytes: possible involvement of thrombin and protease-activated receptors. *Int J Mol Med.* 2006;17(4):551-558.

38. Knutsen G, Drogset JO, Engebretsen L, et al. A randomized trial comparing autologous chondrocyte implantation with microfracture. Findings at five years. *J Bone Joint Surg Am.* 2007;89(10):2105-2112.

39. Kreuz PC, Muller S, Freymann U, et al. Repair of focal cartilage defects with scaffold-assisted autologous chondrocyte grafts: clinical and biomechanical results 48 months after transplantation. *Am J Sports Med.* 2011;39(8):1697-1705.

40. Krishnan SP, Skinner JA, Bartlett W, et al. Who is the ideal candidate for autologous chondrocyte implantation? *J Bone Joint Surg Br.* 2006;88(1):61-64.

41. Kurkijarvi JE, Nissi MJ, Kiviranta I, Jurvelin JS, Nieminen MT. Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) and T2 characteristics of human knee articular cartilage: topographical variation and relationships to mechanical properties. *Magn Reson Med.* 2004;52(1):41-46.

42. Lee KT, Lee YK, Young KW, Park SY, Kim JS. Factors influencing result of autologous chondrocyte implantation in osteochondral lesion of the talus using second look arthroscopy. *Scand J Med Sci Sports.* 2011.

43. Mandelbaum B, Browne JE, Fu F, et al. Treatment outcomes of autologous chondrocyte implantation for full-thickness articular cartilage defects of the trochlea. *Am J Sports Med.* 2007;35(6):915-921.

44. Marcacci M, Kon E, Zaffagnini S, et al. Arthroscopic second generation autologous chondrocyte implantation. *Knee Surg Sports Traumatol Arthrosc.* 2007;15(5):610-619.

45. Marcacci M, Zaffagnini S, Kon E, Visani A, Iacono F, Loreti I. Arthroscopic autologous chondrocyte transplantation: technical note. *Knee Surg Sports Traumatol Arthrosc.* 2002;10(3):154-159.

46. Marlovits S, Singer P, Zeller P, Mandl I, Haller J, Trattnig S. Magnetic resonance observation of cartilage repair tissue (MOCART) for the evaluation of autologous chondrocyte transplantation: Determination of interobserver variability and correlation to clinical outcome after 2 years. *Eur J Radiol.* 2006;57(1):16-23.

47. Marlovits S, Striessnig G, Resinger CT, et al. Definition of pertinent parameters for the evaluation of articular cartilage repair tissue with high-resolution magnetic resonance imaging. *Eur J Radiol.* 2004;52(3):310-319.

48. Marlovits S, Zeller P, Singer P, Resinger C, Vecsei V. Cartilage repair: generations of autologous chondrocyte transplantation. *Eur J Radiol.* 2006;57(1):24-31.

49. Messier SP, Gutekunst DJ, Davis C, DeVita P. Weight loss reduces knee-joint loads in overweight and obese older adults with knee osteoarthritis. *Arthritis Rheum.* 2005;52(7):2026-2032.

50. Micheli L, Curtis C, Shervin N. Articular cartilage repair in the adolescent athlete: is autologous chondrocyte implantation the answer? *Clin J Sport Med.* 2006;16(6):465-470.

51. Micheli LJ, Browne JE, Erggelet C, et al. Autologous chondrocyte implantation of the knee: multicenter experience and minimum 3-year follow-up. *Clin J Sport Med.* 2001;11(4):223-228.

52. Niemeyer P, Pestka JM, Kreuz PC, et al. Characteristic complications after autologous chondrocyte implantation for cartilage defects of the knee joint. *Am J Sports Med.* 2008;36(11):2091-2099.
53. Niemeyer P, Pestka JM, Salzmann GM, Sudkamp NP, Schmal H. Influence of cell quality on clinical outcome after autologous chondrocyte implantation. *Am J Sports Med.* 2012;40(3):556-561.
54. Niemeyer P, Salzmann G, Steinwachs M, et al. Presence of subchondral bone marrow edema at the time of treatment represents a negative prognostic factor for early outcome after autologous chondrocyte implantation. *Arch Orthop Trauma Surg.* 2010;130(8):977-983.
55. Ossendorf C, Kaps C, Kreuz PC, Burmester GR, Sittinger M, Erggelet C. Treatment of posttraumatic and focal osteoarthritic cartilage defects of the knee with autologous polymer-based three-dimensional chondrocyte grafts: 2-year clinical results. *Arthritis Res Ther.* 2007;9(2):R41.
56. Patel AA, Donegan D, Albert T. The 36-item short form. *J Am Acad Orthop Surg.* 2007;15(2):126-134.
57. Petersen W, Zelle S, Zantop T. Arthroscopic implantation of a three dimensional scaffold for autologous chondrocyte transplantation. *Arch Orthop Trauma Surg.* 2008;128(5):505-508.
58. Peterson L. Chondrocyte transplantation. In: DW J, ed. *Master Techniques in Orthopaedic Surgery Reconstructive Knee Surgery*. 2nd Ed ed. Philadelphia (PA): Lippincott, Williams, and Wilkins; 2003:353–374.
59. Peterson L, Brittberg M, Kiviranta I, Akerlund E, Lindahl A. Autologous chondrocyte transplantation. Biomechanics and long-term durability. *American Journal of Sports Medicine.* 2002;30(1):2-12.
60. Peterson L, Minas T, Brittberg M, Nilsson A, Sjogren-Jansson E, Lindahl A. Two- to 9-year outcome after autologous chondrocyte transplantation of the knee. *Clinical Orthopaedics & Related Research.* 2000(374):212-234.
61. Peterson L, Vasiliadis HS, Brittberg M, Lindahl A. Autologous chondrocyte implantation: a long-term follow-up. *Am J Sports Med.* 2010;38(6):1117-1124.
62. Pietschmann MF, Horng A, Niethammer T, et al. Cell quality affects clinical outcome after MACI procedure for cartilage injury of the knee. *Knee Surg Sports Traumatol Arthrosc.* 2009;17(11):1305-1311.
63. Reinold MM, Wilk KE, Macrina LC, Dugas JR, Cain EL. Current concepts in the rehabilitation following articular cartilage repair procedures in the knee. *J Orthop Sports Phys Ther.* 2006;36(10):774-794.
64. Riegger-Krugh CL, McCarty EC, Robinson MS, Wegzyn DA. Autologous chondrocyte implantation: current surgery and rehabilitation. *Med Sci Sports Exerc.* 2008;40(2):206-214.
65. Robertson WB, Fick D, Wood DJ, Linklater JM, Zheng MH, Ackland TR. MRI and clinical evaluation of collagen-covered autologous chondrocyte implantation (CACI) at two years. *The Knee.* 2007;14(2):117-127.
66. Ronga M, Grassi FA, Bulgheroni P. Arthroscopic autologous chondrocyte implantation for the treatment of a chondral defect in the tibial plateau of the knee. *Arthroscopy.* 2004;20(1):79-84.
67. Roos E, Engelhart L, Ranstam J, et al. ICRS Recommendation Document : Patient-Reported Outcome Instruments for Use in Patients with Articular Cartilage Defects. *Cartilage.* 2011;2(2):122-136.
68. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes.* 2003;1(1):64.

69. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS) - development of a self-administered outcome measure. *Journal of Orthopaedic & Sports Physical Therapy.* 1998;28(2):88-96.

70. Saris DB, Dhert WJ, Verbout AJ. Joint homeostasis. The discrepancy between old and fresh defects in cartilage repair. *J Bone Joint Surg Br.* 2003;85(7):1067-1076.

71. Saris DB, Vanlauwe J, Victor J, et al. Treatment of symptomatic cartilage defects of the knee: characterized chondrocyte implantation results in better clinical outcome at 36 months in a randomized trial compared to microfracture. *Am J Sports Med.* 2009;37 Suppl 1:10S-19S.

72. Tiderius CJ, Tjornstrand J, Akeson P, Sodersten K, Dahlberg L, Leander P. Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC): intra- and interobserver variability in standardized drawing of regions of interest. *Acta Radiol.* 2004;45(6):628-634.

73. Trattnig S, Millington SA, Szomolanyi P, Marlovits S. MR imaging of osteochondral grafts and autologous chondrocyte implantation. *Eur Radiol.* 2007;17(1):103-118.

74. Trattnig S, Pinker K, Krestan C, Plank C, Millington S, Marlovits S. Matrix-based autologous chondrocyte implantation for cartilage repair with Hyalograft((R))C: Two-year follow-up by magnetic resonance imaging. *Eur J Radiol.* 2006;57(1):9-15.

75. Welsch GH, Mamisch TC, Zak L, et al. Evaluation of cartilage repair tissue after matrix-associated autologous chondrocyte transplantation using a hyaluronic-based or a collagen-based scaffold with morphological MOCART scoring and biochemical T2 mapping: preliminary results. *Am J Sports Med.* 2010;38(5):934-942.

76. Wondrasch B, Zak L, Welsch GH, Marlovits S. Effect of Accelerated Weightbearing After Matrix-Associated Autologous Chondrocyte Implantation on the Femoral Condyle on Radiographic and Clinical Outcome After 2 Years: A Prospective, Randomized Controlled Pilot Study. *Am J Sports Med.* 2009.

77. Wright RW. Knee injury outcomes measures. *J Am Acad Orthop Surg.* 2009;17(1):31-39.

78. Zaslav K, Cole B, Brewster R, et al. A prospective study of autologous chondrocyte implantation in patients with failed prior treatment for articular cartilage defect of the knee: results of the Study of the Treatment of Articular Repair (STAR) clinical trial. *Am J Sports Med.* 2009;37(1):42-55.

TABLE 1. Descriptive statistics of baseline clinical scores, surgical parameters and 5-year outcome variables in 104 patients.

	Mean (SD) or n (%)*	Range
Baseline Characteristics		
KOOS (Sport/Rec)	23.6 (24.1)	0 - 100
KOOS (QOL)	29.4 (21.3)	0 - 100
Age (years)	37.9 (11.6)	13 - 62
Female	42 (40.5)*	N/A
Body Mass Index	26.7 (3.9)	16.8 – 39.5
SF-36 (MCS)	51.4 (10.3)	23.3 – 85.6
SF-36 (PCS)	39.2 (9.6)	22.0 – 58.6
Duration symptoms (years)	8.4 (7.5)	1 - 46
Number of prior procedures	1.4 (1.2)	0 - 4
Surgical Characteristics		
Defect size (cm)	3.2 (2.3)	0.6 – 10.0
Lateral compartment (vs medial)	30 (28.9)*	N/A
Concomitant surgical procedure	14 (13.5)*	N/A
12 week time to FWB (vs 8 week)	56 (53.9)*	N/A
5-year Outcomes		
KOOS (Sport/Rec)	63.1 (27.1)	0 - 100
KOOS (QOL)	58.5 (23.1)	0 - 100
MRI Composite Score	3.0 (0.7)	1.2 – 4.0
Satisfaction Score	76.2 (25.6)	0 - 100

KOOS = Knee Injury and Osteoarthritis Outcome Score; Sport/Rec = Sport and Recreation; QOL = Quality of Life; SF-36 = 36 item Short Form Health Survey; MCS = Mental Component Score; PCS = Physical Component Score; FWB = full weight bearing; MRI = magnetic resonance imaging.

Table 2. Univariable (conditioning on baseline score) and multivariable linear regression models for the KOOS Sport and Recreation (Sport/Rec) subscale.

Predictor Variable	Univariable		Final Multivariable (Adjusted R^2 0.246)		
	B (95% CI)	P value	B (95% CI)	Standardized beta	P value
Baseline score	0.48 (0.28, 0.68)	<0.001	0.33 (0.12, 0.55)	0.296	0.003
Age (years)	-0.34 (-0.76, 0.07)	0.102			
Female	-2.11 (-12.10, 7.89)	0.741			
Body Mass Index	-0.07 (-1.30, 1.16)	0.912			
SF-36 (MCS)	0.43 (-0.06, 0.92)	0.085	0.52 (0.04, 0.99)	0.185	0.035
SF-36 (PCS)	0.54 (-0.01, 1.08)	0.053	0.63 (0.09, 1.16)	0.222	0.022
Duration symptoms (years)	-0.53 (-1.17, 0.10)	0.100	-0.67 (-1.29, -0.05)	-0.185	0.036
Number of prior procedures	-0.93 (-4.90, 3.04)	0.643			
Time to FWB (8 vs 12 weeks)	-7.69 (-17.39, 2.01)	0.119			
Concomitant surgical procedure	-0.91 (-15.0, 13.2)	0.898			
Defect size (cm)	0.04 (-2.06, 2.13)	0.972			
Graft compartment (lateral vs medial)	3.66 (-6.99, 14.31)	0.497			

SF-36 = 36-item Short Form Health Survey; MCS = Mental Component Score; PCS = Physical Component Score; FWB = full weight bearing.

Table 3. Univariable (conditioning on baseline score) and multivariable linear regression models for KOOS Quality of Life (QOL) subscale.

Predictor Variable	Univariable		Multivariable (Adj R^2 0.139)		Final Model (Adj R^2 0.134)		
	B (95% CI)	P value	B (95% CI)	P value	B (95% CI)	Standardized beta	P value
Baseline score	0.41 (0.22, 0.61)	<0.001	0.41 (0.22, 0.61)	<0.001	0.41 (0.21, 0.60)	0.384	<0.001
Age (years)	-0.08 (-0.45, 0.28)	0.659					
Female	-2.71 (-11.31, 5.88)	0.533					
Body Mass Index	-0.02 (-1.09, 1.06)	0.977					
SF-36 (MCS)	0.42 (-0.02, 0.85)	0.059	0.42 (-0.02, 0.85)	0.059			
SF-36 (PCS)	0.31 (-0.18, 0.80)	0.214					
Duration symptoms (years)	-0.38 (-0.93, 0.18)	0.181					
Number of prior procedures	-1.87 (-5.31, 1.57)	0.284					
Time to FWB (8 vs 12 weeks)	-0.46 (-8.99, 8.06)	0.914					
Concomitant surgical procedure	5.84 (-6.36, 18.05)	0.345					
Defect size (cm)	0.05 (-1.78, 1.88)	0.958					
Graft compartment (lateral vs medial)	2.45 (-6.78, 11.7)	0.600					

SF-36 = 36-item Short Form Health Survey; MCS = Mental Component Score; PCS = Physical Component Score; FWB = full weight bearing.

Table 4. Univariable and multivariable linear regression models for the Magnetic Resonance Imaging (MRI) Composite Score.

Predictor Variable	Univariable		Multivariable (Adj R^2 = 0.159)		Final Model (Adj R^2 = 0.154)		
	B (95% CI)	P value	B (95% CI)	P value	B (95% CI)	Standardized beta	P value
Age (years)	-0.014 (-0.025, -0.003)	0.017	-0.008 (-0.019, 0.003)	0.158			
Female	-0.124 (-0.402, 0.154)	0.378					
Body Mass Index	-0.011 (-0.045, 0.024)	0.546					
SF-36 (MCS)	0.012 (-0.002, 0.026)	0.086	0.013 (-0.001, 0.025)	0.071	0.014 (0.001, 0.027)	0.194	0.036
SF-36 (PCS)	0.000 (-0.014, 0.014)	0.976					
Duration of symptoms (years)	-0.024 (-0.041, -0.006)	0.009	-0.021 (-0.039, -0.002)	0.027	-0.027 (-0.043, -0.010)	-0.292	0.002
Number of prior procedures	-0.114 (-0.223, -0.004)	0.043	-0.045 (-0.156, 0.066)	0.423			
Time to FWB (8 vs 12 weeks)	0.074 (-0.198 ,0.345)	0.593					
Defect size (cm)	-0.078 (-0.135, -0.020)	0.008	-0.076 (-0.131, -0.021)	0.007	-0.083 (-0.137, -0.029)	-0.276	0.003
Concomitant surgical procedure	0.110 (-0.28, 0.51)	0.579					
Graft compartment (lateral vs medial)	-0.094 (-0.393, 0.205)	0.536					

SF-36 = 36-item Short Form Health Survey; MCS = Mental Component Score; PCS = Physical Component Score; FWB = full weight bearing.

Table 5. Univariable and multivariable tobit regression models for the Satisfaction Score.

Predictor Variable	Univariable		Multivariable (pseudo R^2 = 0.010)		Final Model (pseudo R^2 = 0.076)		
	B (95% CI)	P value	B (95% CI)	P value	B (95% CI)	Standardized beta	P value
Age (years)	-0.23 (-0.80, 0.35)	0.439					
Female	-3.49 (-18.61, 11.63)	0.651					
Body Mass Index	-0.05 (-1.77, 1.67)	0.957					
SF-36 (MCS)	0.52 (-0.17, 1.21)	0.140					
SF-36 (PCS)	0.68 (0.00, 1.36)	0.048	0.56 (-0.15, 1.27)	0.123			
Duration of symptoms (years)	-0.40 (-1.50, 0.70)	0.478					
Number of prior procedures	-3.12 (-8.72, 2.48)	0.274					
Time to FWB (8 vs 12 weeks)	-14.85 (-27.98, -1.73)	0.027	-13.01 (-25.93, 0.09)	0.048	-14.85 (-27.98,-1.73)	-0.225	0.027
Defect size (cm)	-0.55 (-2.99, 1.89)	0.658					
Concomitant surgical procedure	5.49 (-14.27, 24.65)	0.598					
Graft compartment (lateral vs medial)	7.19(-9.54, 23.92)	0.337					

SF-36 = 36-item Short Form Health Survey; MCS = Mental Component Score; PCS = Physical Component Score; FWB = full weight bearing.