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Research Article

Matrix induced autologous chondrocyte implantation in the knee: Comparison between osteochondritis dissecans and osteonecrosis and effect of chondrocyte thickness on prognosis

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ABSTRACT

Objective: The aim of this study was compare the clinical success of treatments for avascular necrosis and osteochondritis dissecans in cases who underwent matrix autologous chondrocyte implantations, and evaluate cartilage thickness on the clinical outcomes after implantation.

Methods: A total of 37 patients (29 men, and 8 women; mean age: 23.8 years (16–38)) were treated prospectively with a two-stage matrix autologous chondrocyte implantation (avascular necrosis, n=21; osteochondritis dissecans, n=18). Clinical improvements and follows-up were assessed based on the patients' International Cartilage Repair Society (ICRS) scores with simultaneous cartilage thickness measurement using short-TI inversion recovery magnetic resonance imaging. The patients were divided into four subgroups based on their clinical scores, as group D <65 points, Group C 65–83 points, Group B 84–90 and Group A ≥90.

Results: The mean ICRS score was 28.33±7.14 in the preoperative period in the avascular necrosis group, which increased to 70.88±12.61 at 60 months; while the mean ICRS score increased from 29.75±7.15 preoperatively to 87.58±12.83 at 60 months in the osteochondritis dissecans group. A statistically significant difference in the ICRS scores was noted between the two groups, and also between the ICRS scores and cartilage thicknesses of the subgroups ($p<0.05$).

Conclusion: Our study results revealed that greater clinical improvement was achieved in patients with osteochondritis dissecans undergoing matrix autologous chondrocyte implantation than in those with avascular necrosis. In addition, cartilage thickness greater than 3.7 mm following an autologous chondrocyte transplantation showed excellent clinical improvement.

Level of Evidence: Level III, Therapeutic Study

The avascular structure of cartilage and the insufficient number of differentiated cell damages confined to the cartilage cannot heal due to the absence of bleeding and fibrin clotting. In such cases, only chondrocytes show limited proliferation, thereby increasing the synthesis of matrix macromolecules at the damage site. Given that, the new matrix and cells cannot restore the surface (1, 2). The repaired tissues have lower levels of stiffness and durability when compared to normal hyaline cartilage (1-3, 4).

In pathological processes where there was a loss of a significant cartilage surface of 3 to 4 cm^2, the symptoms decrease activity levels and the quality of life, specifically in younger patients. This inevitably leads to treatment (1-4). Accordingly, the treatment of progressive lesions along with large cartilage loss is one of the most significant unmet needs. Previous studies, in general, agree on the safety and efficacy of autologous chondrocyte implantations (ACI) in isolated cartilage defects larger than 4 cm^2 (5-8).

Evaluations of the metabolic changes that occur in tissues through magnetic resonance imaging (MRI) with T1 and T2 mapping are effective in directing treatment (9). MRI with T2 mapping is the only source of information on the biomechanical and morphological characteristics of the developing cartilage tissue and collagen integration (10-15).

In this study, we compare the clinical successes of the treatment between avascular necrosis (AVN)

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and osteochondritis dissecans (OCD) in cases who underwent matrix ACI (MACI) and evaluate cartilage thickness based on the clinical outcomes after implantation.

This study compared the clinical success between avascular necrosis and osteochondritis dissecans cases who underwent matrix autologous chondrocyte implantation in international cartilage research society grade four osteochondral cartilage defects. Furthermore, cartilage thickness on clinical outcomes after matrix autologous chondrocyte implantation was investigated.

The primary hypothesis is that a clinically and statistically signific ant difference could be expected in the midterm outcomes of AVN and OCD cases who underwent MACI. The secondary hypothesis was that clinical and radiologic outcomes and results between cartilage thickness and clinical outcomes would be comparable in all groups with statistical significance at the midterm follow-up.

Materials and Methods

This study included 37 patients who were diagnosed with clinical stage IV osteochondral defects as per the International Cartilage Repair Society criteria between 2006 and 2010. Patients with chronic inflammatory arthritis, instability of the knee joint, prior meniscectomy, body mass index (BMI) >26 kg/m^2, deformities of the varus >3˚and valgus >5˚, early osteoarthritis, patellar malalignment, chondrocalcinosis and those who were lost to follow-ups were excluded from the study. During the study, one patient was excluded as he did not attend the follow-up visits regularly, and one patient was excluded due to heart attack-related mortality at four years.

Of the 37 patients included in the study (19 AVN with bilateral diseases in two cases and 18 OCD), two patients had cartilage damage in both knees as a sequela of AVN. The etiology of AVN in all patients was because of steroid use. Four patients were treated for gastrointestinal diseases, while15 were treated for hematological diseases. Once the remission of the primary disease was achieved, the AVN patients received surgery.

The mean cartilage defect size was 7.54±1.80 cm^2(4.2–10.5 cm^2) (Table 1). The mean articular defect size of the AVN group was 1.195±0.12 cm, and the mean articular defect size of the OCD group was 1.18±0.101 cm (Table 2).The mean follow-up was 72.4 months (range: 5 to 9 years). All patients were followed using the ICRS knee-scoring scale. The cartilage defect was 23(58%) patients at medial femoral condyle and 16 patients (42%) at lateral femoral condyle (Table 1).

The patients were divided into four subgroups based on their clinical scores and the differences of cartilage thicknesses on the short-TI inversion recovery (STIR) MRI were compared. Patients with ≤65 points were assigned to the negative outcome group (Group D), 65–83 points to the moderate outcome group (Group C), 84–90 to the good outcome group (Group B), and ≥90 points to the excellent group (Group A). We used the Kruskal-Wallis test to non-parametrically compare the cartilage thicknesses with the subgroup scores. The subgroups were compared according to the cartilage defect size, perfusion mrg vascularity, and cartilage thickness. There were significant results only regarding cartilage thickness.

Table 1. Demographic and clinical characteristic of patients

N	**37 patients; 39 knees**
Male N (%)	29 (78.3)
Female N (%)	8 (21.3)
Mean Age	23.8 (16–38)
Mean BMI kg/m^2	23.4 (20–26)
Mean Durationof Symptoms	1.3 year
MFC	23 (58%)
LFC	16 (42%)
Size (cm)	7.54±1.80 cm^2 (4.2–10.5 cm^2)

MFC: medial femoral condyle; LFC: lateral femoral condyle; OCD: osteochondritis dissecans; AVN: avascular necrosis

Table 2. Characteristic features of Osteochondritisdissecans and avascular necrosis

	OCD	**AVN**	**Statistical difference Independent T-samples**
N	19 (56%) (Two cases were bilateral)	18 (44%)	
Depth of lesion (cm)	1.195±0.12	1.18±0.101	(p<0.001)
Age	24.20±7.65	23.33±7.98	(p=0.0021)
Lesion size (cm^2)	7.66±1.88	7.10±2.01	(p=0.0034)

All patients were evaluated preoperatively and at 6, 12, 24, and 60 months. Furthermore, we obtained T2 mapping MRIs using a Siemens 1.5 T Avanto device (Siemens, Erlangen, Germany) at the predefined time points, and measured cartilage thicknesses. The MRI scans were evaluated by two radiologists who were blinded to the study groups. Cartilage thickness was measured at the thickest region of the operation field from three different points, and their means were calculated. The mean cartilage thicknesses of both knees were calculated for the patients with bilateral AVN knee lesions.

We used the Statistical Package for Social Sciences version 20.0 (IBM Corp.; Armonk, NY, USA) software for the statistical analysis, which was done at 99% so that a confidence interval is obtained as %0.01.

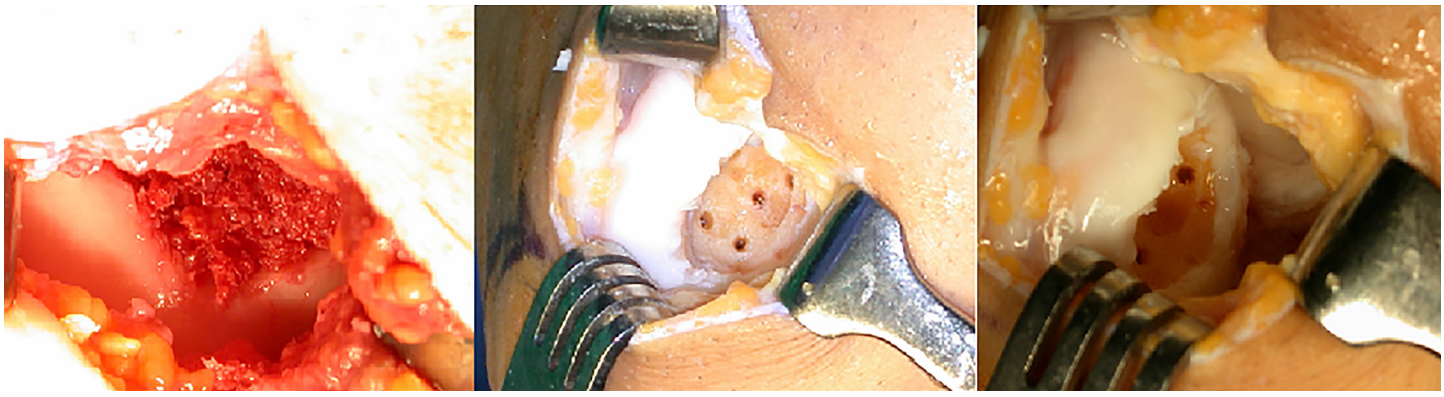

Figure 1. Curetted osteochondral defect, bone floor was perforated and impaction of spongious graft press-fit to the femoral condyle

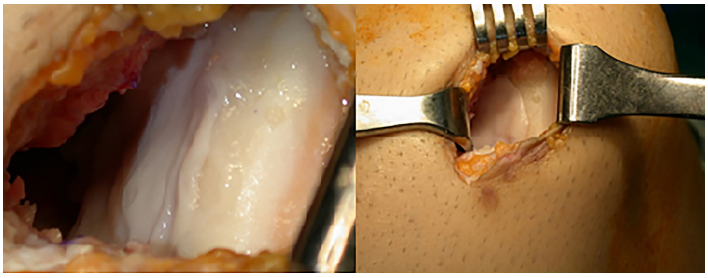

Figure 2. Appearance in a case whounderwent implantation (second stage)

Surgical technique

A single surgeon, who is the senior author of this study (Binnet MS), operated on all patients. All patients received a two-stage surgery. In the first stage, lesions at the joint cartilage and accompanying intra-articular findings were documented through an arthroscopic intervention and chondral biopsy samples were taken. Joint mice that became mobile were removed in six patients during arthroscopy. Based on the arthroscopy findings, the cartilage defects were exposed by a parapatellar-limited arthrotomy during the same session, either medially or laterally, according to the location of the lesion (Figure 1). Autologous cancellous bone grafts harvested from the iliac crest were used in all patients. After the chondrocyte cultures, which were prepared in the initial operation, grew and were ready for implantation at six weeks, the second stage was initiated. No graft resorption was observed in any of the patients during either radiological examination or surgery. The same patellar incision was performed again, and the MACI was inserted on the subchondral layer over the defect and fixed with fibrin gel (Figure 2). No sutures were used in any patients for the fixation of the cartilage tissues. After the first and second stages of the operation, full range of motion (ROM) and quadriceps-strengthening exercises were instructed in the fourth week. After the second operation, partial weight-bearing was allowed at six weeks, and full weight-bearing at 12 weeks.

All patients were informed about the nature of the tissue transplantation and written informed consent was obtained. Ankara University Medical School Ethics Committee (No. 2004/52-1283) approved the study protocol, and the study was conducted as per the principles of the Declaration of Helsinki.

Results

The OCD and AVN groups were compared with an independent t-sample test in terms of mean age and lesion dimensions, and no significant difference was found in the mean age (p=0.0021) or mean area of cartilage damage (p=0.0034). In this regard, the groups were homogenous regarding age and cartilage defect area (Table 1, 2). The overall final patient follow-up was 100% after the patients who did not regularly attend the clinical visits were excluded from the study.

A T2 mapping MRI of all patients was made preoperatively. At 6, 12, 24, and 60 months the remodeled cartilage thicknesses were measured (Figure 3, 4). In the postoperative measurements of all patients, the mean cartilage thicknesses were 1.99±1.07 mm at 6 months, 2.17±1.03 mm at 12 months, 2.16±1.11 mm at 24 months, and 2.25±1.12 mm at 60 months. According to the Freidman test, the change in K-values (cartilage thickness: mm) between each measurement month was not statistically significant (p=0.644). Although cartilage thicknesses measured by a T2 mapping MRI after MACI showed an increase at 6 months, the increase was not statistically significant.

According to the independent samples t-test (p=0.541), no statistically significant difference was found between the AVN and OCD groups preoperatively. Comparing the 6^{th}, 12^{th}, 24^{th}, and 60^{th} month based on the independent samples t-test (p<0.001), however, revealed significant differences in the MRI cartilage thicknesses and ICRS clinical scores. Furthermore, the OCD patients who received MACI had both thicker cartilage and better clinical outcomes than the AVN patients did (Table 3, Figure 5).

In the evaluation of the postoperative six-month ICRS scores, a comparison of the four groups in separate evaluations regarding ICRS scores with a Kruskal-Wallis test did not show significant differences (p=0.772). When the ICRS scores and cartilage thicknesses at the postoperative 12^{th} month were evaluated separately among the groups, significant differences were found between the A, B, C, and D Groups from the Kruskal-Wallis test (p<0.001). When the ICRS scores and cartilage thicknesses in the postopera-

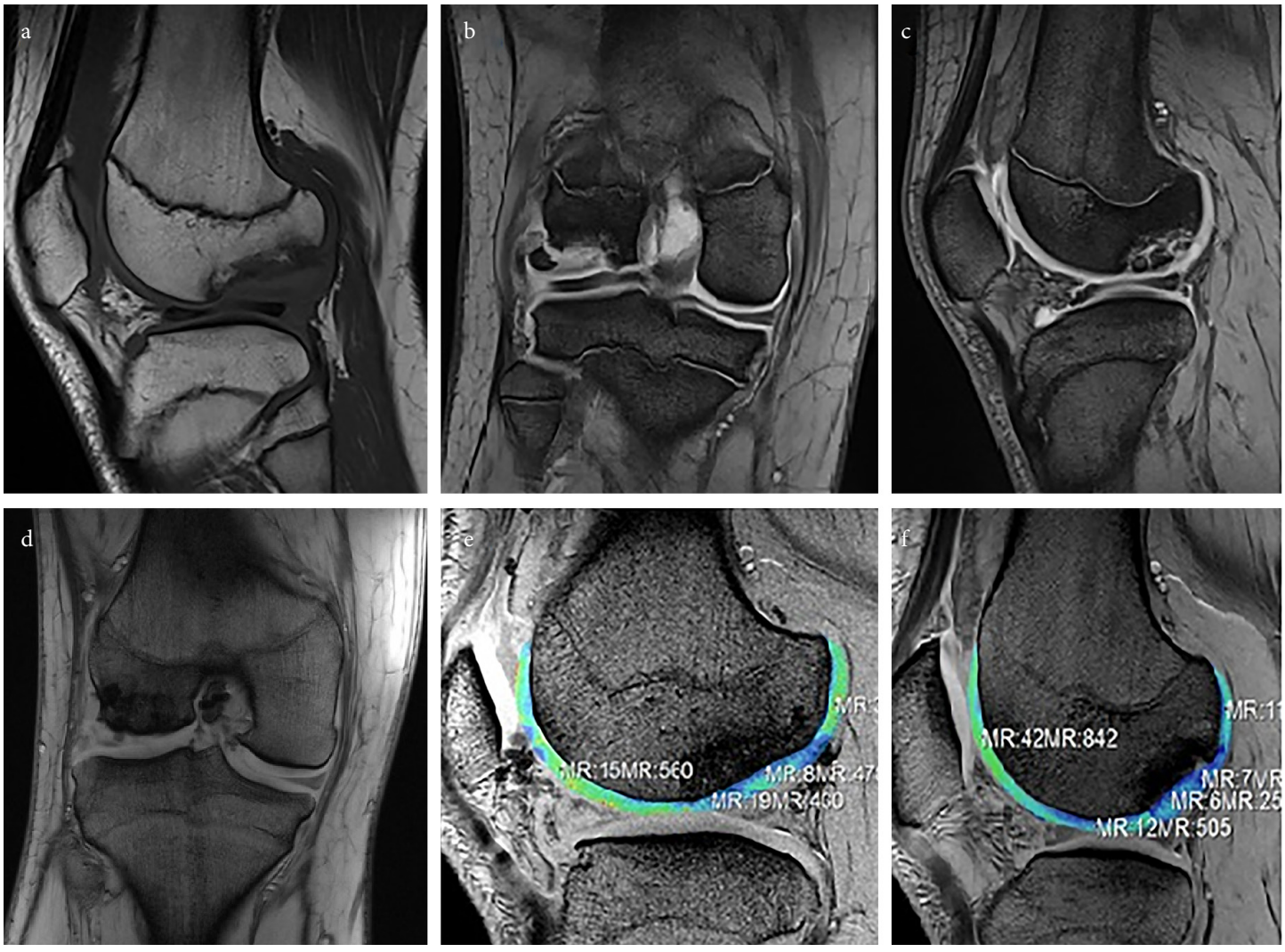

Figure 3. a-f. A 16-year-old male patient withOCD. Irregularity in the joint surface at the femoral lateral condyle with sagittal proton density image, and an irregular area with low signal intensity (a). Irregularity at the cartilage surface at the femoral lateral condyle and approximate osseous fragment displaced laterally on thecoronal and sagittal T2-weighted images (b, c). Postoperative first-year coronal MRI (d). Postoperative second-year (e). Postoperative fifth-year cartilage thicknesses on STIR MRI (f)

tive 24th month were evaluated separately among the groups, significant differences were found between the A, B, C, and D groups from a Kruskal-Wallis test (p=0.006). In an evaluation of the ICRS scores and cartilage thicknesses in the postoperative 60th month among the groups separately, significant differences were found between the A, B, C, and D Groups from a Kruskal-Wallis test (p=0.005) (Table 3).

All patients were divided into four groups according to their clinical scores, and these were analyzed according to their scores and cartilage thicknesses at STIR MRI. Those who had 65 points or less were grouped in the negative outcome group (Group D), 65–83 points were grouped in the moderate outcome (Group C), 84–90 points in the good outcome group (Group B), and 90< points in the perfect group (Group A). We used the Kruskal-Wallis test to non-parametrically compare the cartilage thicknesses with the subgroup scores.

The mean cartilage thickness in Group A at the 6th month was 3.4 mm (1 OCD/0 AVN); in Group B, it was 2.6±0.53 mm (5 OCD/2 AVN); in Group C, 1.6±0.37 mm (8 OCD/11 AVN); and in Group D 1.1±0.58 mm (4 OCD/6 AVN). In the evaluation of postoperative 6th-month ICRS scores, a comparison of the four groups in separate evaluations regarding ICRS scores with the Kruskal-Wallis test did not show significant differences (p=0.772). The mean cartilage thickness in Group A at the 12th month was 3.9±0.16 mm (4 OCD/0 AVN), while in Group B it was 2.8±0.49 mm (8 OCD/3 AVN), in Group C it was 1.5±0.52 mm (4 OCD/12 AVN), and in Group D it was 1.3±0.22 mm (2 OCD/4 AVN). When ICRS scores and cartilage thicknesses at the postoperative 12th month were evaluated separately among groups, significant differences were found between Groups A, B, C, and D Groups with the Kruskal-Wallis test (p<0.001). The mean cartilage thickness in Group A at the 24th month was 3.6±0.14 mm (5 OCD/0 AVN), while in Group B it was 2.9±0.47 mm (8 OCD/4 AVN), in Group C it was 1.7±0.38 mm (5 OCD/12 AVN), and in Group D it was 1.4±0.2

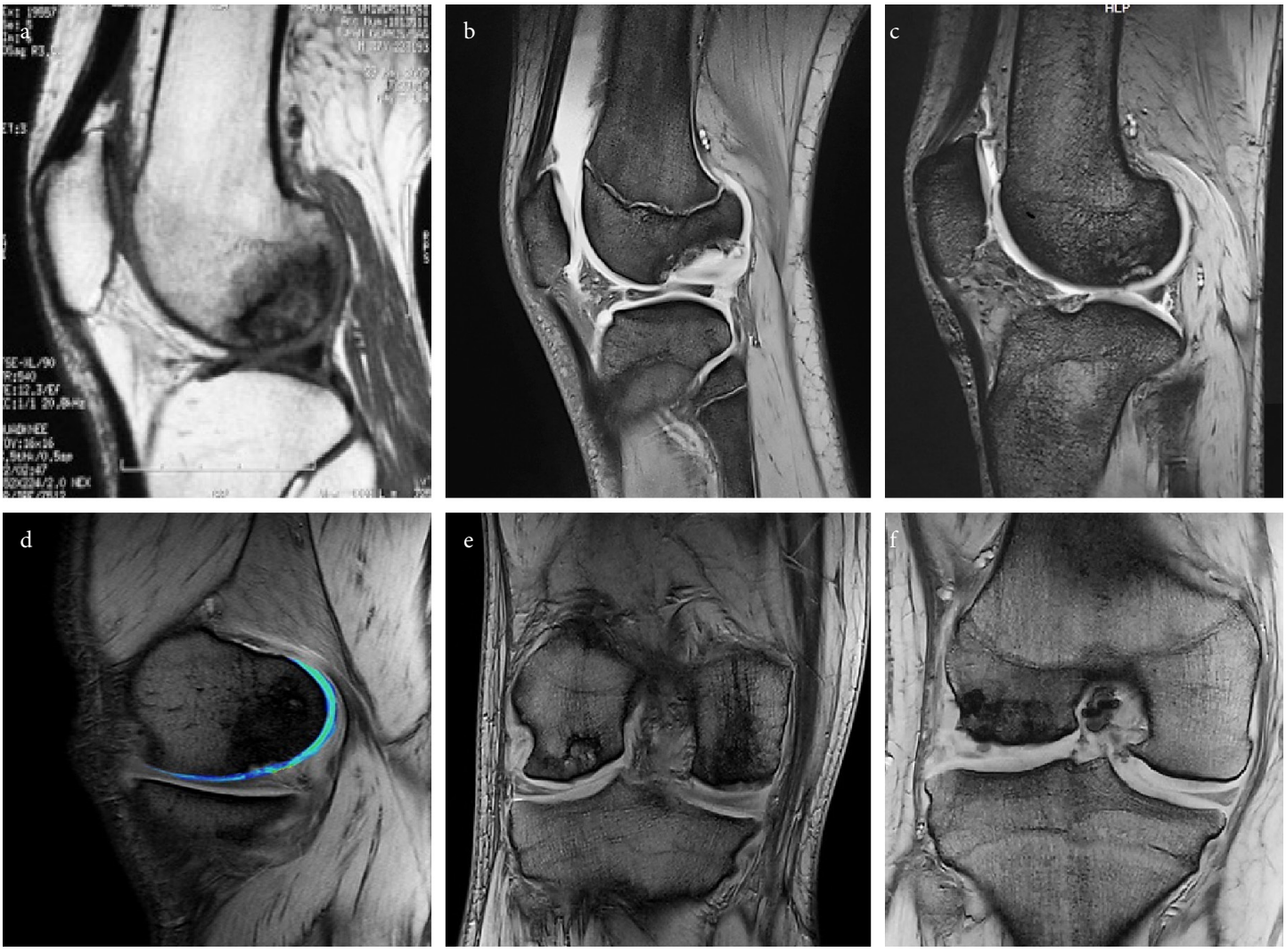

Figure 4. a-f. A 39-year-old male patient with AVN. Diagnosed with osteonecrosis due to Crohn's disease and cortisone use (a, b). Postoperative third-yearsagittal imaging, an avascular area with low signal intensity (c, d). Postoperative fifth-year coronal imaging, irregularity in the cartilage surface and osseous fragment (e, f)

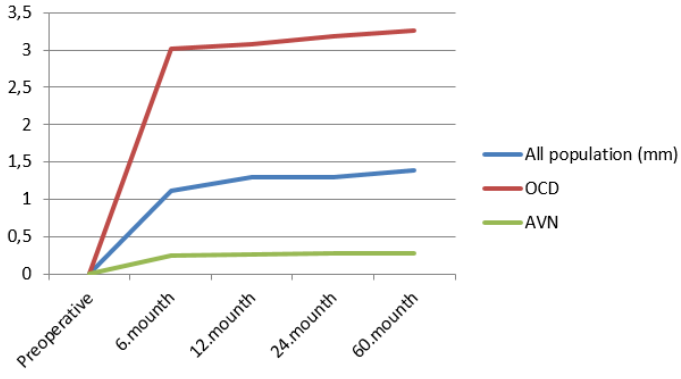

Figure 5. Mean cartilage thicknesses of all patients, AVN and OCD on MRI measurement

Horizontal line: months; Perpendicular line: cartilage thickness as mm

mm (0 OCD/3 AVN). When ICRS scores and cartilage thicknesses at the postoperative 24th month were evaluated separately among groups, significant differences were found between Groups A, B, C, and D groups with the Kruskal-Wallis test (p=0.006). In the evaluation of ICRS scores and cartilage thicknesses at the postoperative 60th month among groups separately, significant differences were found between A, B, C, and D Groups with the Kruskal-Wallis test (p=0.005). The mean cartilage thickness in Group A at the 60th month was 3.7±0.15 mm (5 OCD/0 AVN), while in Group B it was 2.7±0.29 mm (8 OCD/4 AVN), in Group C it was 1.7±0.32 mm (5 OCD/12 AVN), and in Group D it was 1.4±0.2 mm (0 OCD/3 AVN). The cartilage thickness measurements after autologous chondrocyte transplantation with MRI showed parallelism with the clinical scores. A cartilage thickness over 3.7 mm after autologous chondrocyte transplantation is in parallel with an excellent clinical improvement .

A cartilage thickness of over 3.7 mm after an autologous chondrocyte transplantation indicated an excellent clinical improvement.

None of the patients had early postoperative complications, although a progressive limitation of motion occurred in three pa-

Table 3. Clinical scores and cartilage thicknesses of the AVN and OCD groups

Groups	ICRS Score mean values	Independent samples T-test for ICRS between two groups	Cartilage thickness mean values (mm)	Independent samples T-test for cartilage thickness between two groups
Preop. AVN	28.33±7.14	p=0.541	-	-
Preop. OCD	29.75±7.15		-	-
PO. 6th month AVN	60.22±10.79	p<0.001	1.12±0.33	p<0.001
PO. 6th month OCD	74.48±12.44		3.01±0.64	
PO.12th month AVN	66.51±12.55	p<0.001	1.39±0.49	p<0.001
PO.12th month OCD	85.66±13.70		3.08±0.67	
PO.24th month AVN	70.84±13.12	p<0.001	1.30±0.46	p<0.001
PO.24th month OCD	86.03±12.47		3.18±0.69	
PO.60th month AVN	70.88±12.61	p<0.001	1.39±0.53	p<0.001
PO.60th month OCD	87.58±12.83		3.26±0.65	

AVN: avascular necrosis; OCD: osteochondritis dissecans; PO: postoperative; Preop: preoperative

Table 4. Management approaches and failures

Problem	Postoperative Months	Treatment	N
Delamination at healing tissues after trauma AVN(1 case)	2	Repeating MACI	1
Arthrofibrosis OCD (1 case), AVN (2 cases)	3,4,4	Arthroscopic release, Debridement, Aggressive Physical Therapy and Rehabilitation	3
Patellofemoral pain OCD (1 case), AVN (2 cases)	3,4,6,6,7	Aggressive Physical Therapy and Rehabilitation	5

tients in the midterm, and the rehabilitation team monitored these patients. Full ROM was achieved in one of these patients after long-term rehabilitation, while arthrofibrosis that occurred in the other two patients was repaired by an arthroscopic debridement and release procedure. After surgery and aggressive rehabilitation, full ROM was obtained in one patient, despite a persistent weakness of the quadriceps muscle. No positive outcome was achieved in the other patient after aggressive rehabilitation, and so, an arthrotomy and release procedure was performedone year later, although a flexion loss of 40° persisted.

Graft delamination occurred in one patient (AVN) eight weeks after MACI due to a fall-induced rotational knee trauma. This patient consented to a second MACI, and a two-stage MACI was re-performed. The delaminated graft was removed in the first intervention, the biopsy procedure was repeated, and a hematoma was removed from the joint. In the second intervention, MACI was applied again, and the patient underwent preventive rehabilitation, after which, clinical improvement was achieved after three months (Table 4).

Discussion

This study identified a significant correlation between clinical scores and cartilage thicknesses in patients who underwent MACI. We also compared the MRI scans and clinical scores of the patients who underwent MACI for OCD and AVN. When the patients with OCD and AVN were combined into a single group and the clinical scores were analyzed with the cartilage thicknesses by an STIR MRI, and cartilage thicknesses were compared non-parametrically with clinical groups according to ICRS scores with a Kruskal-Wallis test, all control groups showed significant differences in cartilage thickness. The mean cartilage thickness was 3.7 mm in the patients with ≥90 ICRS points.

During the follow-up with T2 mapping, an organization of the zonal cartilage tissues was observed 1.5 years after ACI (12). Ebert et al. used the Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) classification system with the MRI and clinical scores during a two-year follow-up of patients (n=47) who underwent MACI for patellofemoral defects (5). The authors recorded an increase in MOCART scores in parallel with an increase in the

duration of the follow-ups. The MOCART classification test is used with MRI where scoring depends on the morphological images of the healing cartilage tissues on MRI. Cartilage thickness is not measured directly but compared with the adjacent intact cartilage tissue (16, 17). The patients had no fibrillation, fissure, ulcerations, subchondral lamina damage, or subchondral bone changes in the autograft cartilage tissues described for the MOCART system. The MOCART scoring system was originally developed for all osteochondral induction systems and is not specific for MACI. There, however, is still no classification system after MACI treatment. We hope that the measurement of cartilage thickness will evolve to a new calcification system after MACI.

There is still a lack of consensus on the optimum follow-up of patients undergoing chondrocyte transplantation. A second-look arthroscopy could be conducted considering the relevant studies in the literature, although there are ethical issues to performing arthroscopy at each control visit. Furthermore, a decision could be given based on an assessment of the softness of the tissue with the probe during arthroscopy. An objective decision cannot be reached about the quality of chondral tissue.

The most important finding of the study is that the etiological factor affects clinical success in patients treated with MACI. Patients with OCD achieve higher clinical scores and thicker cartilage compared to those having AVN. In this study, when the clinical scores in the postoperative period after MACI for AVN and OCD etiology were compared for different months, the patients who underwent MACI after OCD had statistically significantly higher scores than those in the AVN group. There were also significant differences in the cartilage thicknesses of these two groups at the predefined control time points, based on cartilage measurements with STIR MRI. Cartilage thicknesses were also greater in OCD patients. Although there are many methods, and successful results have been reported in the literature after MACI in cases with extensive cartilage defects, there has been no study to date comparing treatment outcomes after MACI for OCD and AVN, which are seen most frequently in the young patient population.

Clinical success in patients with OCD undergoing MACI is higher than in patients with AVN, and cartilage thickness at the implantation site is thicker in patients with OCD. Although clinical follow-up is possible in the follow-up after autologous chondrocyte transplantation with two-stage MACI, cartilage thickness measurements with STIR MRI over the operation area are also significant. Specifically, a cartilage thickness of over 2.7 mm at a STIR MRI is a good clinical outcome, while over 3.7 mm is an excellent clinical outcome. In our study, however, nine patients had different complications. Five patients had patellofemoral pain, three patients had arthrofibrosis (OCD/1 patient had rehabilitation and AVN/2 patients had arthroscopic debridement and release procedure), and one patient had graft delamination. The patient who had graft delamination had moderate ICRS scores.

There are some limitations associated with this study, with one of the most significant being the small sample size and the lack of cartilage thickness measurements via biopsy through a second-look arthroscopy, which is impossible due to ethical issues. In the MRIs of patients with osteonecrosis, an under perfusion of the spongious bone, i.e. insufficient vascularization of the bone autograft, might be present, although further studies are needed to clarify this issue. Mature cartilage tissue might not grow due to insufficient perfusion and nutrition in an undernourished autograft implantation site. In this study, we examined only the presence or absence of bone resorption in the spongious bone impaction areas. Bone autograft implantation might be evaluated through scintigraphic imaging modalities in patients with AVN after MACI, although further studies are required to shed light on any changes in the viability of the bone autografts. There with, another limitation of the study is that there were no control groups. It, however, was a serious ethical problem to untreated patients with OCD or AVN.

In conclusion, the results of this study suggest that two-stage autologous chondrocyte transplantation with MACI is an effective and safe method in extensive ICRS Stage four cartilage damage. Clinical improvements after treatment and high clinical scores can be achieved within the first year. Furthermore, no significant decreases in clinical scores were observed during the five-year follow-up of the patients. Clinical success in patients with osteochondritis dissecans undergoing MACI is higher than patients with avascular necrosis, and cartilage thickness at the implantation site is thicker in patients with OCD. Although clinical follow-up is possible in the follow-up after autologous chondrocyte transplantation with two-stage MACI, cartilage thickness measurements with STIR MRI over the operation area are also significant. Specifically, a cartilage thickness over 2.7 mm at STIR MRI is a good outcome, and over 3.7 mm is an excellent clinical outcome.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Ankara University Medical School Ethics Committee (No. 2004/52-1283).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Author Contributions: Concept - M.S.B., K.B., M.A.; Design - M.A., M.S.B.; Supervision - M.S.B., K.B., M.Arıkan; Resources - M.A., M.Arıkan; Materials - M.A., M.Y., M.S.B.; Data Collection and/or Processing - M.A., M.A., M.Y., M.S.B.; Analysis and/or Interpretation - M.A., M.Arıkan, M.S.B.; Literature Search - M.A., M.S.B.; Writing Manuscript - M.A., M.Arıkan, M.S.B.; Critical Review - M.S.B.

Conflict of Interest: The authors have no conflicts of interest to declare.

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