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The use of autologous chondrocyte implantation following and combined with anterior cruciate ligament reconstruction

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Abstract We report our experience of using autologous chondrocyte implantation (ACI) to treat osteochondral defects of the knee in combination with anterior cruciate ligament (ACL) reconstruction. The outcome of symptomatic osteochondral lesions treated with ACI following previous successful ACL reconstruction is also reviewed. Patients were followed for a mean of 23 months. Nine patients underwent ACL reconstruction in combination with ACI. Mean modified Cincinnati knee scores improved from 42 to 69 following surgery. Seven patients described their knee as better and two as the same. A second group of nine patients underwent ACI for symptomatic articular cartilage defects following previous ACL reconstruction. In this group, the mean modified Cincinnati knee score improved from 53 to 62 after surgery. Six patients described their knee as better and three as worse. Combined treatment using ACI with ACL reconstruction is technically feasible and resulted in sustained improvement in pain and function. The results following previous ACL reconstruction also resulted in clinical improvement, although results were not as good as following the combined procedure.

Résumé Nous rapportons notre expérience de la greffe autologue de chondrocytes (ACI) pour traiter les lésions ostéochondrales du genou en combinaison avec la reconstruction du LCA. Le résultat du traitement par ACI des lésions ostéochondrales symptomatiques, après un bon

résultat de la reconstruction précédente du LCA est aussi examiné. Les malades ont été suivis en moyenne 23 mois. Neuf malades ont eu une intervention combinée. La moyenne du score modifié de Cincinnati s'est améliorée de 42 à 69 après la chirurgie. Sept malades ont décrit leur genou comme meilleur et deux comme le même. Un deuxième groupe de neuf malades a subi une greffe de chondrocytes pour lésion symptomatique du cartilage articulaire après une reconstruction du LCA. Dans ce groupe, la moyenne du score modifié de Cincinnati s'est améliorée de 53 à 62 après l'intervention. Six malades ont décrit leur genou comme meilleur et trois comme pire. Le traitement combiné qui utilise la greffe de chondrocyte avec la reconstruction du LCA est techniquement faisable et a apporté une amélioration notable de la douleur et de la fonction. L'intervention effectuée après la reconstruction antérieure du LCA apporte une amélioration clinique, bien que les résultats ne soient pas aussi bons qu'après la procédure combinée.

Introduction

Anterior cruciate ligament (ACL) rupture and articular cartilage injury can produce disabling symptoms such as pain and instability in young individuals, with progression to osteoarthritis in the long term [6]. Damage to the articular surface commonly accompanies rupture of the ACL [10], occurring either at the time of the initial injury or secondary to chronic instability. The incidence of articular cartilage injury in acute ACL injuries ranges from 15% to 40% [5, 10], whereas in chronic deficiency it has been reported to be as high as 77% [3]. The possibility of occult articular cartilage injury at the time of ACL rupture has been suggested by the demonstration of bone bruising in up to 80% of cases by magnetic resonance imaging (MRI). This phenomenon may be a predictor of future cartilage degeneration, even in the absence of a visible defect [9, 12, 13, 17, 25].

When damaged, articular cartilage has a limited capacity to repair itself, and the resultant fibrocartilage lacks the

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biomechanical loadbearing properties of hyaline cartilage. Treatment modalities for osteochondral defects of the knee include debridement [26], abrasion chondroplasty [18], microfracture [27], allograft transplantation [7], periosteal transplantation [22], autograft transplantation [16], and autologous chondrocyte implantation (ACI) [23]. However, only the latter two result in hyaline-like repair. At our institution, we have had six years of experience with ACI. Good to excellent clinical results have been reported by the majority of authors using this technique [4, 23, 24]. The original method of cell implantation described by Brittberg et al. [4] involved injecting the cultured autologous chondrocytes under a sutured periosteal patch. More recent variations of the technique include the use of a type I–III collagen porcine membrane [2, 14] and the use of a type I–III collagen bilayer seeded with chondrocytes—matrix-induced autologous chondrocyte implantation (MACI) [8].

The few studies that describe combined treatment of osteochondral defects in the ACL-deficient knee have employed autologous periosteum [21], autologous osteochondral grafting [1, 3, 5], or periosteum-covered ACI (p-ACI) [23]. In this study we report the preliminary findings of ACL reconstruction in combination with collagen-covered ACI (c-ACI) and MACI. We also report on the outcome of a second group of patients with previous history of successful ACL reconstruction who, without interceding injury, presented to our institution with symptomatic full-thickness chondral defects that were treated with ACI.

Patients and methods

Using a prospective database of patients treated with ACI under the auspices of the four senior authors over a 5-year period, we identified two groups of patients (see Tables 1 and 2). The groups were independent, and the outcome from each was considered separately.

Group 1 consisted of nine patients (five men, four women) who underwent a combined procedure of ACL reconstruction (seven hamstring autograft, two bone-

patella-bone autograft) and autologous chondrocyte implantation (six MACI, three c-ACI). All patients complained of pain, and six also reported instability. The average age at the time of surgery was 32.2 years (range 21–45). The anatomical sites of the defects were medial femoral condyle (seven), lateral femoral condyle (one), and trochlea (one), with a mean area of 3.11 cm² (range 1–6 cm²). The mechanism of injury was of a sporting nature in eight patients and unknown in one patient. The mean time from injury to surgery was 97.9 months (range 18–185), reflecting the initial conservative treatment of six patients. All patients had undergone previous arthroscopy and presented to our unit with known ACL ruptures. The osteochondral defect was diagnosed before referral in seven patients, of whom three had been treated with chondral shaving (two) or mosaicplasty (one). Other earlier surgical procedures included partial medial meniscectomy (two), partial lateral meniscectomy (two), and Herbert screw fixation of an osteochondral fragment (one).

Group 2 consisted of nine patients (eight men, one woman) who presented with symptomatic full-thickness osteochondral defects, which were treated with c-ACI. Each patient had undergone previous successful ACL reconstruction (five hamstring autograft, four bone-patella tendon-bone autograft) and presented with stable knees. The average age at the time of surgery was 35.1 years (range 28–51). The anatomical sites of the defect were the medial femoral condyle (five), lateral femoral condyle (one), trochlea (two), and patella (one), with a mean area of 2.23 cm² (range 1–6 cm²). The mean time from ACL reconstruction to ACI was 58.7 months (range 12–120). Two patients (cases 1 and 2) were referred to our unit with known osteochondral defects that had been unsuccessfully treated with drilling at the time of ACL reconstruction, with the patients describing continued pain and disability. The remaining seven patients presented without history of further interim trauma but with symptoms of progressive knee pain. In the interim period, there were six further procedures, including arthroscopy (three), medial meniscectomy (two), and osteochondral drilling (one).

Table 1 Group 1 patient summary (*VAS* visual analogue score, *SC* Stanmore functional rating system, *MC* modified Cincinnati score, *c-ACI* chondroguide-assisted autologous chondrocyte implantation, *MACI* matrix-associated chondrocyte implantation, *h-ACL* hamstring autograft ACL reconstruction, *p-ACL* bone-patella tendon-bone autograft ACL reconstruction, *MFC* medial femoral condyle, *LFC* lateral femoral condyle)

Patient	Age/ sex	Combined procedure	Injury to surgery (months)	Defect size (cm ²)/site	Follow-up (months)	<u>VAS</u>		<u>SC</u>		<u>MC</u>	
						Preoperative	Follow-up	Preoperative	Follow-up	Preoperative	Follow-up
1 AG	39/F	c-ACI/h-ACL	185	3 Trochlea	37	3	0	2	0	51	68
2 LM	45/F	c-ACI/h-ACL	180	1.5 MFC	24	7	2	3	1	44	78
3 NJ	28/F	c-ACI/h-ACL	84	5.3 MFC	23	7	2	3	1	34	60
4 KP	31/M	MACI/h-ACL	156	6 MFC	23	6.5	4	3	3	56	58
5 WS	32/M	MACI/h-ACL	150	2 MFC	23	6	0	3	0	45	91
6 CT	35/M	MACI/h-ACL	60	1 MFC	20	6	3	2	2	30	49
7 RD	21/M	MACI/h-ACL	48	2.5 MFC	23	3	3	2	1	41	95
8 TW	22/M	MACI/p-ACL	20	3.75 LFC	13	6	3	3	1	38	56
9 KM	37/F	MACI/p-ACL	18	3 MFC	12	2	0	4	0	41	68

Table 2 Group 2 patient data (*VAS* visual analogue score, *SC* Stanmore functional rating system, *MC* modified Cincinnati score, *c-ACI* chondroguide-assisted autologous chondrocyte implantation, *h-ACL* hamstring autograft ACL reconstruction, *p-ACL* bone-patella tendon-bone autograft ACL reconstruction)

Patient	Age/ sex	ACL technique	Time from ACL reconstruction to c-ACI (months)	Defect size (cm ²)/site	Follow-up (months)	<u>VAS</u>		<u>SC</u>		<u>MC</u>	
						Preoperative	Follow-up	Preoperative	Follow-up	Preoperative	Follow-up
1 ML	27/M	h-ACL	12	2.3 LFC	16	6	1	2	1	59	87
2 RJ	51/M	h-ACL	12	1.5 MFC	42	2	6	3	3	66	38
3 ADL	38/M	h-ACL	36	3 Troch	39	4.5	3	2	0	58	76
4 AB	29/M	h-ACL	36	2 MFC	21	5	3	3	1	43	87
5 CM	30/M	h-ACL	60	1 MFC	47	8	3	4	1	38	71
6 BA	39/M	p-ACL	60	6 MFC	27	6.5	6.5	3	4	66	26
7 JM	37/M	p-ACL	96	1.6 Patella	28	6	1	3	0	61	84
8 MH	28/M	p-ACL	96	1.5 MFC	48	4.5	7	3	4	31	18
9 NE	37/F	h-ACL	120	1.2 Troch	12	5	3	3	1	53	74

Preoperative evaluation

All patients were subject to a clinical, radiographic, and arthroscopic examination. The modified Cincinnati (MC) rating system and Stanmore functional rating system (Fig. 1) were the primary outcome measures employed. The MC system was subdivided into a clinical grading system: excellent (>80), good (55–79), fair (30 to 55), and poor (<30). In addition, we recorded a visual analogue score (VAS) in which, on a scale of 0–10, 0 represents no pain and 10 represents the worst pain ever experienced. We also asked patients to grade their outcome as better, the same, or worse.

Surgical technique

At the initial arthroscopy, if the condition was considered suitable for ACI, a small biopsy of nonweightbearing articular cartilage (medial trochlea) was taken and the cells sent for processing by Verigen Transplantation Services. Following satisfactory culture, the second stage was carried out 4 weeks later, either isolated (group 2) or combined with ACL reconstruction (group 1). Previously described implantation techniques were employed for c-ACI (20) and MACI (22). With respect to the combined procedure, the ACL reconstruction was performed first using either a

hamstring (seven) or bone-patella tendon-bone graft (two), followed by cell implantation (Fig. 2).

Rehabilitation

The first two patients to undergo the combined procedure were immobilised in plaster of Paris postoperatively for one week. However, in both cases this led to problems with joint stiffness and required manipulation of the knee under anaesthetic. Subsequently, patients were subject to continuous passive motion for the first 48 h postoperatively. Our protocol for patients in group 2 involved immobilisation in a cylinder cast for one week, following which a physiotherapy-led rehabilitation protocol was instituted. Patients were gradually mobilised and fully weightbearing by six weeks. We advised avoidance of strenuous sporting activities for 12 months.

Follow-up

All patients were followed up at six weeks, six months, one year, and annually thereafter. This involved clinical assessment and evaluation with the previously documented scoring systems.

Fig. 1 Stanmore functional rating system

0	No pain
1	Slight pain after vigorous activity; sport/work/Activities of daily living NOT affected
2	Mild pain after limited activity; sport/work/Activities of daily living ARE affected
3	Moderate pain after limited activity; sport/work/Activities of daily living ARE affected
4	Severe pain with activity or rest pain

Fig. 2 Perioperative photograph showing autologous chondrocyte implantation and anterior cruciate ligament grafts in situ

Results

Patient demographics and outcomes are summarised in Tables 1 and 2. A comparison of the mean modified Cincinnati scores in the two groups is depicted in Fig. 3.

Group 1

The average follow-up for group 1 was 22 months (range 12–37). The mean VAS preoperatively was 5.4 (range 3–7), improving to 1.9 (range 0–6.5) at final follow-up. The mean modified Cincinnati score preoperatively was 42.2 (range 30–56), improving to 69.2 (range 34–95) at final follow-up (Table 1). According to this grading system, at final follow-up there were two excellent outcomes, six good, and one fair. Subjective evaluation revealed seven patients describing their knee as better and two as the same (cases 4 and 6). According to the Stanmore rating system, all patients scored 0 (no pain) or 1 (slight pain after vigorous activity), except case 6, who scored 2 (mild pain after limited activity), and case 4, who scored 3 (moderate pain after

limited activity), which suggested that activities of daily living were affected.

Group 2

The average follow-up for group 2 was 31.1 months (range 12–48). The mean VAS preoperatively was 5.27 (range 2–8), improving to 3.38 (range 1–7) at final follow-up. The mean modified Cincinnati score preoperatively was 52.7 (range 31–66), improving to 62.3 (range 18–87) at final follow-up (Table 2). According to the clinical grading system, at final follow-up there were three excellent, three good, one fair, and two poor outcomes. This correlated with the subjective assessment and the Stanmore scores, such that six patients described their knee as better and three as worse.

Two patients in group 1 required manipulation under anaesthetic for postoperative stiffness. Otherwise, there were no major complications in either group.

Discussion

Good to excellent results were observed in eight out of nine patients in group 1. These short-term results support the combined treatment of a torn ACL and symptomatic osteochondral defect using c-ACI or MACI.

Matsusue et al. [21] first reported combining treatment of an osteochondral lesion with ACL reconstruction. They used an arthroscopic osteochondral autograft technique, which was replicated by Bobic [3] in a series of 12 patients. He reported satisfactory results in ten patients at two years follow-up. Klinger et al. [19] studied 21 patients treated with autologous osteochondral grafting and ACL reconstruction and reported good outcomes in 19 patients. The success reported in these studies must be tempered by the fact that recent evidence from a randomised controlled trial suggests that cartilage repair following autologous osteochondral autografting is inferior to ACI [2]. In a review of seven patients undergoing autologous periosteum transplantation with ACL reconstruction at two years follow-up, Alfredson et al. [1] reported one excellent, five good, and one poor clinical outcome using the Brittberg scoring system. However, these results must also be viewed cautiously because autologous periosteum transplantation has not gained widespread acceptance for treating osteochondral defects of the knee.

Periosteum-covered ACI (p-ACI) has been successfully performed in combination with ACL reconstruction. At an average of 4 years follow-up, Peterson et al. [24] reported good results in 12 out of 16 patients (75%) with isolated femoral condyle defects. However, this represented a higher failure rate compared with the treatment of isolated femoral condyle defects. Significant disadvantages of p-ACI, particularly when used in combination with ACL reconstruction, include the risk of arthrofibrosis and the increased tourniquet time for periosteal harvesting. In contrast to both p-ACI and c-ACI, in which suturing the scaffold can be particularly time-consuming, implantation

Fig. 3 Progression of mean modified Cincinnati score over time in the two groups

of the MACI membrane is suture-free and therefore quicker [8]. This offers significant benefit with regards to reduction in anaesthetic and tourniquet time. ACL reconstruction and ACI are both expensive procedures that are associated with a prolonged period of postoperative limitation [20]. Performing ACL reconstruction in combination with ACI of MACI in carefully selected patients, rather than as a staged procedure, may potentially be less costly.

In the case of a full-thickness cartilage defect in an ACL-deficient knee, a number of factors need to be addressed before considering treatment. The fate of the ACL-injured knee, whether reconstructed or not, has been reported to culminate in degenerative arthritis [11, 15]. However, restoring functional stability remains vitally important in this young and active group of patients. If a symptomatic chondral lesion is diagnosed before ligamentous reconstruction, a two-stage procedure with initial chondrocyte harvesting and combined surgery 4–6 weeks later can be performed. If the lesion is small ($<1\text{ cm}^2$) and is detected coincidentally, a more conservative approach, possibly with a marrow stimulation technique, can be considered, especially if the symptoms are not clearly attributable to the lesion.

A recent study evaluated the natural history of untreated osteochondral defects in patients undergoing ACL reconstruction, using a control group of patients without articular cartilage injury. The subjective findings showed a statistically significant difference in favour of the defect group, although the mean scores overall in both groups indicated that most patients had few symptoms. There was no difference in the objective findings [25]. However, it was unclear whether these patients were symptomatic from the chondral defect. Without scientific evidence supporting treatment of asymptomatic lesions, careful patient selection is required before embarking on a combined procedure. In chronic deficiency, a symptomatic chondral lesion requires treatment. It must be remembered that when considering treatment of such a lesion, asymptomatic instability with an ACL rupture should still be an indication for reconstruction to protect the graft from shearing and failure [20, 23].

When facing a new chondral lesion in a previously reconstructed ACL (group 2), the integrity of the ligament graft should be ascertained before considering ACI. In our series six patients had good outcomes, whereas three were objectively and subjectively worse. This could be attributed to progressive degenerative disease resulting from the initial ACL rupture, as it is well recognised that reconstruction does not reliably suspend the progression to osteoarthritis.

In conclusion, treatment of an ACL rupture in combination with ACI (c-ACI or MACI) is technically feasible, with good to excellent outcomes in most patients in the short term. The shorter anaesthetic and tourniquet time associated with the use of MACI may make combined treatment using this technique more favourable. The use of ACI and ACL reconstruction in combination, particularly in young patients describing both pain and instability and with aspirations of returning to sporting activities, may offer the best long-term outcome.

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