The Most Common Rehabilitation Protocol After Matrix-Assisted Autologous Chondrocyte Implantation Is Immediate Partial Weight-Bearing and Continuous Passive Motion

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Purpose: To perform a systematic review of postoperative rehabilitation protocols for third-generation autologous chondrocyte implantation (ACI) of the knee joint. **Methods:** A systematic review was performed by searching PubMed, Cochrane Library, and EMBASE to locate randomized controlled trials that described a rehabilitation protocol following third-generation ACI of the knee joint. The search terms used were: "autologous" AND "chondrocyte" AND "randomized". Data extracted from each study included various components of postoperative rehabilitation, such as initial weight-bearing (WB) status and time to full WB, the use of continuous passive motion (CPM), the time to return to sports, and physical therapy (PT) modalities used and the timing of their initiation. **Results:** Twenty-five studies (22 Level I, 3 Level II) met inclusion criteria, including a total of 905 patients undergoing treatment with ACI. The average patient age ranged from 29.1 to 54.8 years, and the mean follow-up time ranged from 3 months to 10.0 years. The average lesion size ranged from 1.9 to 5.8 cm^2, and the most common lesion location was the medial femoral condyle (n = 494). Twenty studies allowed partial WB postoperatively with all studies permitting full WB within 12 weeks. Twenty studies used CPM in their rehabilitation protocols and initiated its use within 24 hours postoperatively. Among 10 studies that reported time to return to sport, 9 (90%) allowed return by 12 months. While most protocols used strength training as well as the inclusion of proprioceptive training, there was disagreement on the timing and inclusion of specific PT modalities used during the rehabilitation process. **Conclusions:** Based on the included studies, most rehabilitation protocols for third-generation ACI initiate CPM within 24 hours postoperatively and allow partial WB immediately following surgery with progression to full WB within 12 weeks. There is variation of the PT modalities used as well as the timing of their initiation. **Level of Evidence:** Level II, systematic review of Level I-II studies.

Focal chondral defects (FCDs) of the knee joint can result in pain and swelling and may become especially disruptive to active patients and athletes.[1] Cartilage defects are challenging to treat, given the avascularity of articular cartilage and the multiple factors that affect cartilage health, including meniscal status, limb alignment, and ligament stability.[2] Current surgical treatments for FCDs of the knee joint include chondroplasty, microfracture (MFx), osteochondral autograft transfer (OAT), osteochondral allograft transplantation (OCA), and autologous chondrocyte implantation (ACI), among others.[3] ACI, which is a 2-stage procedure, is now in its third-generation form, which is otherwise known as matrix-assisted ACI.[4]

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Third-generation ACI involves taking a biopsy of healthy articular cartilage during the first-stage procedure, followed 6 to 8 weeks later by implantation of a matrix scaffold seeded with autologous chondrocytes.[4]

Given that third-generation ACI is a relatively novel procedure, postoperative rehabilitation following this procedure is not standardized.[5] In a 2018 systematic review, Kraeutler et al.[5] compared treatment failure rates and other clinical outcomes of matrix-assisted ACI based on the time to return to full weight-bearing (WB). However, this is just one aspect of postoperative rehabilitation, and other aspects, such as the use of continuous passive motion (CPM) and criteria for return-to-play (RTP), are equally important in determining a patient's overall outcome and satisfaction. The purpose of this study was to perform a systematic review of postoperative rehabilitation protocols for third-generation ACI of the knee joint. The authors hypothesized that there would be heterogeneity in the postoperative rehabilitation protocols reported in the literature.

Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines using a Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist. Two independent reviewers (J.D., S.M.F.) searched PubMed, Embase, and the Cochrane Library up to January 17, 2022. The electronic search strategy used was: *autologous* AND *chondrocyte* AND *randomized*. A total of 652 studies were reviewed by title and/or abstract to determine study eligibility based on inclusion criteria. In cases of disagreement, a third reviewer (M.J.K.) made the final decision. Inclusion criteria included randomized controlled trials that reported their rehabilitation protocol after third-generation ACI for FCDs of the knee joint. Studies were excluded if they were nonrandomized, studies on first- or second-generation ACI, nonhuman studies, non-knee joint studies, the rehabilitation protocol was not reported, or no English full-text article was available. Data extraction from each study was performed independently by 2 authors (J.D., S.M.F.) and then reviewed by a third author (M.J.K.). There was no need for funding or a third party to obtain any of the collected data. Risk of bias was assessed according to the Cochrane Collaboration's risk of bias tool,[6] which incorporates an assessment of randomization, blinding, completeness of outcomes data, selection of outcomes reported, and other sources of bias.

Study Methodology Assessment

The Modified Coleman Methodology Score (MCMS)[7] was used to evaluate study methodology quality. The MCMS has a scaled potential score ranging from 0 to 100. Scores ranging from 85 to 100 are excellent, 70 to 84 are good, 55 to 69 are fair, and less than 55 are poor. The primary outcomes assessed by the MCMS are study size and type, follow-up time, attrition rates, number of interventions per group, and proper description of study methodology.

Data Extraction

Data extracted from each study included the various components of postoperative rehabilitation, such as initial WB status and time to full WB, the use of CPM, the time to RTP, and physical therapy modalities used and the timing of their initiation.

Results

Twenty-five studies met inclusion and exclusion criteria (Fig 1), including a total of 905 patients undergoing treatment with ACI. The mean patient age ranged from 29.1 to 54.8 years and the mean follow-up ranged from 3 months to 10.0 years. The overall percentage of male subjects ranged from 44.4% to 74.2% and the mean body mass index ranged from 23.3 to 29.0 (Table 1). The mean lesion size ranged from 1.9 to 5.8 cm^2. The most common lesion location was the medial femoral condyle (n = 494 cases) followed by the lateral femoral condyle (n = 167 cases). Six studies[8-13] presented 2 of the same patient populations and therefore only the studies with longer follow-up[8,10,12] were included in the results of our systematic review.

Postoperative WB

Twenty-two studies[8,10,12,14-32] reported on postoperative WB (Table 2). All but 2 studies[16,17] allowed partial WB immediately after operation. One study[29] allowed full WB at 4 weeks, 9 studies[10,12,15,18,25,26,28,30,32] allowed full WB at 6 weeks, 11 studies[10,16,19-25,27,31] allowed full WB at 8 weeks, and 10 studies[8,12,14,17,19-24] allowed full WB at 10 to 12 weeks' postoperatively. Three studies[10,25,12] consisted of an initial 2-week period of WB at 20%, followed by a progressive increase to full WB at 6 weeks' postoperatively. Eight studies[10,19-25] consisted of a 2-week period of WB at 20%, with a progressive increase to full WB at 8 weeks' postoperatively. One study[12] described a 10-week rehabilitation protocol consisting of toe-touch WB for 4 weeks, followed by partial WB at 20% between weeks 4 and 6, 50% WB between weeks 6 and 8, and full WB by 10 weeks' postoperatively. Five studies[20-24] consisted of a 5-week period of WB at 20% with a progressive increase to full WB at 11 weeks' postoperatively. One study[19] consisted of a 2-week period of WB at 20%, with a progressive increase to full WB at 12 weeks' postoperatively.

Continuous Passive Motion

Eighteen studies[10,12,14-16,18-21,23-28,30-32] used CPM as part of the rehabilitation process for all patients

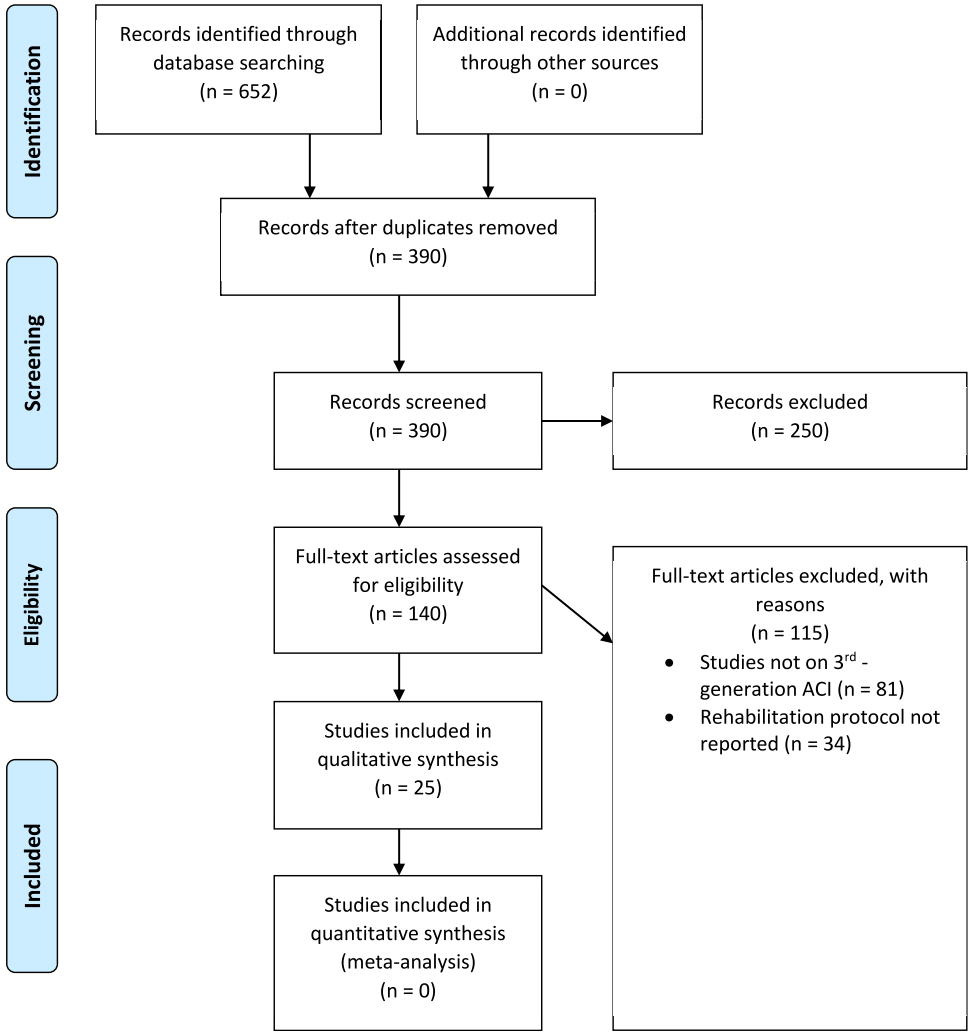

Fig 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. (ACI, autologous chondrocyte implantation.)

included (Table 3). In most studies, CPM was initiated within 12 to 24 hours of surgery with an initial range of motion (ROM) of 0 to 30° of knee flexion.

Return-to-Play

Ten studies[8,10,15,18,21,27,28,30-32] reported on the time to RTP following surgery. In 9 studies,[8,10,15,21,27,28,30-32] RTP was allowed at 12 months after ACI. In one study,[18] sports activity was allowed after 6 months.

Physical Therapy

Thirteen studies[8,10,12,19-21,23-25,27,28,30,31] used isometric exercises as part of their postoperative rehabilitation protocol (Table 4). Ten studies[10,17,20-26,28] described the use of a brace during rehabilitation. Thirteen studies[8,10,12,17,20,21,25-31] stated time to full knee ROM. Three studies[10,21,28] described the use of open-chain exercises. Four studies[10,20,21,25] described the use of closed-chain exercises, with all 4 studies initiating these exercises at 7 weeks postoperatively. Thirteen studies[8,10,12,19-21,23-27,30,31] described the use of progressive strengthening in their rehabilitation protocol. Eight studies[8,10,20,21,25,27,30,31] described the use of neuromuscular (proprioceptive/balance) training. Eight studies[8,10,20,21,25,27,30,31] addressed initiation of sports-specific movements. Eight studies[10,14,19-21,23-25] used cryotherapy to control edema.

Modified Coleman Methodology Score

Table 5 shows the MCMS scores from the 25 included studies. Six studies[10,20,21,28,30,31] received an excellent score, 17 studies[8,9,11-19,22-24,27,29,32] received a good score, and 2 studies[25,26] received a fair score.

Methodologic Quality Assessment

The results of the methodologic quality assessment of included studies using the Cochrane Collaboration's risk of bias tool are presented in Figure 2. Sequence generation and allocation were adequately reported by most studies,[9-25,27,30-32] except in 4 studies,[8,26,28,29] in which the concealment of allocation from the

Table 1. Patient Demographics

Study	LOE	N	Male, %	Age at Surgery, y	BMI	Follow-up, y	Defect Size, cm^2	Lesion Location	Author Country	Type of ACI Product
Akgun et al., 2015[14]	I	7	57	32.7 ± 10.4	24.3 ± 0.8	2	3.0 ± 0.8	MFC: 5; LFC: 2	Turkey	Chondro-Gide
Barié et al., 2020[15]	I	9	44.4	30.4 ± 6.8	23.32 ± 1.15	9.6 ± 0.9	4.27 ± 0.2	MFC: 8; LFC: 1	Germany	BioSeed-C
Basad et al., 2010[16]	I	40	63.0	33.0	25.3	2	NR	C: 29; PT: 11	Germany	ACI-Maix
Saris et al., 2014[11]	I	72	62.5	34.8 ± 9.2	26.2 ± 4.3	2	5.8 ± 5.1	MFC: 48; LFC: 13; T: 4	Netherlands/ Sweden	ACI-Maix
Brittberg et al., 2018[8]										
Clavé et al., 2016[17]	I	30	66.7	29.2 ± 11.9	23.4 ± 3.1	2	3.1 ± 0.8	NR	France	Cartipatch
Crawford et al., 2012[18]	I	21	90.0	41 ± 9	29 ± 3	2	2.9 ± 1.4	NR	U.S.A.	NeoCart
Ebert et al., 2008[24]	I	62	64.5	38.3	NR	3 months	3.3	MFC: 45; LFC: 17	Australia	ACI-Maix
Ebert et al., 2010[23]	I	70	64.3	38.2	NR	2	3.3	MFC: 52; LFC: 18	Australia	ACI-Maix
Ebert et al., 2010[22]	I	61	63.9	38.5	NR	1	3.3	MFC: 46; LFC 15	Australia	ACI-Maix
Ebert et al., 2011[20]	I	69	63.8	38.2	26.6	2	3.3	MFC: 52; LFC: 17	Australia	ACI-Maix
Ebert et al., 2012[21]	I	63	66.7	38.2	26.5	5	3.3	MFC: 47; LFC: 16	Australia	ACI-Maix
Ebert et al., 2020[19]	I	60	65.0	37.6	27.5	10	3.27	MFC: 44; LFC: 16	Australia	ACI-Maix
Ebert et al., 2021[10]	I	37	56.8	36.4	25.7	5	3.0	MFC: 27; LFC: 10	Australia	ACI-Maix
Ebert et al., 2017[9]										
Edwards et al., 2013[25]	I	28	60.7	35.8	25.6	1	2.9	MFC: 20; LFC: 8	Australia	ACI-Maix
Fossum et al., 2019[26]	II	21	66.7	37.2 ± 10.8	25.7 ± 4.3	2	4.9 ± 4.4	MFC: 7; LFC:2; T: 7; P: 1; PT: 2; T-MFC: 2	Norway	Chondro-Gide
Hoburg et al., 2021[27]	I	52	63.5	36 ± 10	25.7 ± 3.3	3	2.2 ± 0.7	C: 52	Germany	Spherox
Ibarra et al., 2021[28]	I	24	70.8	33.7 ± 9.4	25.5 ± 3.1	6.2 ± 0.9	1.9 ± 0.9	MFC: 7: LFC: 9; T: 1; P: 7	Mexico	Neoveil
Liu et al., 2021[29]	I	10	50	54.8 ± 18.0	NR	1.1	2.9 ± 0.8	MFC: 10	Taiwan	Kartigen
Niemeyer et al., 2019[31]	II	52	63.4	36 ± 10	25.7 ± 3.3	2	2.2 ± 0.7	C: 52	Germany	Spherox
Niemeyer et al., 2020[30]	I	75	70.7	33.5 ± 9.2	25.2 ± 3.1	4	5.0 ± 1.9	C: 28; P: 47	Germany	Spherox
Wondrasch et al 2009[13]	I	31	74.2	33	24.7	2	4.8	MFC: 22; LFC: 10	Austria	HyalograftC
Wondrasch et al. 2015[12]										
Zeifang et al., 2010[32]	II	11	54.5	29.1 ± 7.5	NR	2	4.3 ± 1.1	NR	Germany	BioSeed-C

NOTE. Only the nonoverlapping patient samples are included to avoid redundancy. Sex is reported as a percentage. Age, BMI, follow-up, and defect size are reported as mean ± SD (if available).

ACI, autologous chondrocyte implantation; BMI, body mass index; C, nonspecified femoral condyle; LFC, lateral femoral condyle; LOE, Level of Evidence; MFC, medial femoral condyle; N, number of lesions; NR, not reported, P, patella; PT, patella-trochlea; SD, standard deviation; T, trochlea; T-MFC, trochlea and medial femoral condyle.

Table 2. Postoperative WB

Study	Initial WB Status	Progression to Full WB
Akgun et al., 2015[14]	Partial WB	12 weeks
Barié et al., 2020[15]	Partial WB	6 weeks
Basad et al., 2010[16]	Non-WB	8 weeks
Brittberg et al., 2018[8]	Partial WB	12 weeks
Clavé et al., 2016[17]	Non-WB	10 weeks
Crawford et al., 2012[18]	Partial WB	6 weeks
Ebert et al., 2020[19]	Partial WB	8 weeks/12 weeks*
Ebert et al., 2011[20]	Partial WB	8 weeks/11 weeks*
Ebert et al., 2021[10]	Partial WB	6 weeks/8 weeks*
Ebert et al., 2012[21]	Partial WB	8 weeks/11 weeks*
Ebert et al., 2010[22]	Partial WB	8 weeks/11 weeks*
Ebert et al., 2010[23]	Partial WB	8 weeks/11 weeks*
Ebert et al., 2008[24]	Partial WB	8 weeks/11 weeks*
Edwards et al., 2013[25]	Partial WB	6 weeks/8 weeks*
Fossum et al., 2019[26]	Partial WB	6 weeks
Hoburg et al., 2021[27]	Partial WB	8 weeks
Ibarra et al., 2021[28]	Partial WB	6 weeks
Liu et al., 2021[29]	Partial WB	4 weeks
Niemeyer et al., 2020[30]	Partial WB	6 weeks
Niemeyer et al., 2019[31]	Partial WB	8 weeks
Wondrasch et al., 2015[12]	Partial WB	6 weeks/10 weeks*
Zeifang et al., 2010[32]	Partial WB	6 weeks

WB, weight-bearing.
*These studies compared return to full WB at 2 different time points.

investigators was unclear (unclear risk of bias). Fourteen studies[9-15,17-21,30,31] were deemed to be at low risk for detection bias because of the blinding of the outcome assessor, whereas 11 studies[8,16,22-29,32] did not use blinded outcome assessors (high risk of bias). Due to the nature of the study, all patients in all studies were aware of which treatment group they were in (high risk of bias). Three studies[26,31,32] reported a minor loss of follow-up between 10 and 20% without proper explanation (unclear risk of bias), while no other studies reported significant loss of follow-up (low risk of bias).

Discussion

The principal finding of this study was that most studies on third-generation ACI allowed partial WB postoperatively, with all studies progressing to full WB by 12 weeks following surgery. CPM was described in 20 studies and often initiated within 24 hours following the ACI procedure. Most studies allowed a full RTP at 12 months postoperatively. While most protocols used strength training as well as the inclusion of proprioceptive training, there was disagreement on the timing and inclusion of specific physical therapy modalities used during the rehabilitation process. In comparison, MACI (Vericel, Cambridge, MA) has published its own rehabilitation protocol.[33] Patients are mobile with crutches within the first week, and obtain full WB and full knee ROM without a knee brace by 8 to 12 weeks' postsurgery. Isometric exercises are started within 1 to 2 weeks, and sports-like movement and balancing exercises are initiated by 4 weeks. Patients can expect full RTP activity by 9 months. The evidence behind this protocol has been described in detail in one study.[34] The first 6 weeks allow for implantation and protection, the next 6 weeks allow for transition and proliferation, with the subsequent 14 weeks allowing for remodeling and maturation. Ten studies[8,10,16,19-25] followed the Vericel protocol.

Third-generation ACI has garnered significant attention in recent years based on its advantages of using autologous chondrocytes in a scaffold that may be cut to the precise shape of a focal defect. A recent systematic review[35] demonstrated superior outcomes with third-generation ACI compared with MFx, despite a previous systematic review[36] (which included first- and second-generation ACI) showing no outcome differences between ACI and MFx. Furthermore, although ACI is typically considered a second-line treatment option due to its greater cost compared with other cartilage repair options,[3] recent evidence has shown that primary ACI results in improved outcomes compared with ACI following failed marrow stimulation techniques.[37] This lends further credence to the thought of ACI as another first-line treatment option for FCDs. Given the increasing popularity of third-generation ACI, it is important to attempt to standardize the various aspects of perioperative care for these patients, in particular postoperative rehabilitation.

In a 2018 systematic review of 7 randomized controlled trials, Kraeutler et al.[5] compared failure rates and patient-reported outcomes between patients undergoing third-generation ACI based on the time to return to full WB (6, 8, or 10/11 weeks). The authors

Table 3. Continuous Passive Motion (CPM)

Study	Initiation of CPM (Postoperatively)	Initial ROM	Duration of CPM
Akgun et al., 2015[14]	12-24 hours	0°-30°	1 hour/NR
Barié et al., 2020[15]	24 hours	NR	NR/6 weeks
Basad et al., 2010[16]	NR	NR	NR
Crawford et al., 2012[18]	24 hours	NR	NR
Ebert et al., 2020[19]	NR	0°−30°	NR
Ebert et al., 2011[20]	NR	0°−30°	NR/3 weeks
Ebert et al., 2021[10]	12-24 hours	0°−30°	1 hour/NR
Ebert et al., 2012[21]	12-24 hours	0°−30°	NR
Ebert et al., 2010[23]	12-24 hours	0°−30°	NR
Ebert et al., 2008[24]	12-24 hours	0°−30°	1 hour/NR
Edwards et al., 2013[25]	12-24 hours	0°−30°	1 hour/NR
Fossum et al., 2019[26]	NR	NR	4 hours/5 days
Hoburg et al., 2021[27]	24 hours	0°−60°	NR/6 weeks
Ibarra et al., 2021[28]	72 hours	0°−40°	4 hours/NR
Niemeyer et al., 2020[30]	24 hours	0°−60°	NR/6 weeks
Niemeyer et al., 2019[31]	24 hours	0°−60°	NR/6 weeks
Wondrasch et al., 2015[12]	48 hours	0°−40°	3 hours/NR
Zeifang et al., 2010[32]	24 hours	NR	NR/6 weeks

NOTE. Duration of CPM values are reported as hours per day/total number of days or weeks that CPM was used.
NR, not reported; ROM, range of motion.

Table 4. Rehabilitation Protocols

Study	Isometric Exercise	Brace Duration	Time to Full ROM	Open-Chain Exercises	Closed-Chain Exercises	Progressive Strengthening	Neuromuscular Training	Sports-Specific Movements
Brittberg et al., 2018[8]	NR	—	12	—	—	6	12	12
Clavé et al., 2016[17]	—	4	10	—	—	—	—	—
Ebert et al., 2020[19]	NR	—	—	—	—	NR	—	—
Ebert et al., 2011[20]	1	12	5	—	7	4	7	7
Ebert et al., 2021[10]	1	12	5	12	7	4	7	7
Ebert et al., 2012[21]	1	12	7	12	7	7	7	7
Ebert et al., 2010[22]	—	12	—	—	—	—	—	—
Ebert et al., 2010[23]	NR	12	—	—	—	NR	—	—
Ebert et al., 2008[24]	NR	11	—	—	—	NR	—	—
Edwards et al., 2013[25]	1	8	5	—	7	4	7	7
Fossum et al., 2019[26]	—	6	NR	—	—	NR	—	—
Hoburg et al., 2021[27]	NR	—	7	—	—	7	7	7
Ibarra et al., 2021[28]	1	6	6	16	—	—	—	—
Liu et al., 2021[29]	—	—	3 days	—	—	—	—	—
Niemeyer et al., 2020[30]	1	—	7	—	—	7	7	7
Niemeyer et al., 2019[31]	1	—	7	—	—	7	7	7
Wondrasch et al., 2015[12]	1	—	4	—	—	6	—	—

NOTE. Values are reported as time of initiation following surgery (in weeks unless otherwise specified). Brace duration is reported as total number of weeks of brace use.

NR, study reported use of regimen but did not specify initiation time; ROM, range of motion; —, rehab modality was not mentioned.

found no significant differences in treatment failure rates between groups at a mean follow-up of 2.5 years, with significant improvements in Knee Injury and Osteoarthritis Outcome Scores, Short-Form Health Survey, and visual analog scale scores within each group. The present study builds upon this previous systematic review by reviewing additional features of postoperative rehabilitation such as the use of CPM devices and return to sport criteria.

Table 5. Modified Coleman Methodology Score (MCMS)

Study	MCMS
Akgun et al., 2014[14]	75
Barie et al., 2020[15]	76
Basad et al., 2010[16]	82
Brittberg et al., 2018[8]	81
Clavé et al., 2016[17]	82
Crawford et al., 2012[18]	79
Ebert et al., 2012[21]	91
Ebert et al., 2021[10]	88
Ebert et al., 2011[20]	85
Ebert et al., 2017[9]	82
Ebert et al., 2020[19]	82
Ebert et al., 2010[23]	81
Ebert et al., 2010[22]	80
Ebert et al., 2008[24]	80
Edwards et al., 2013[25]	69
Fossum et al., 2019[26]	69
Hoburg et al., 2020[27]	80
Ibarra et al., 2021[28]	85
Liu et al., 2021[29]	70
Niemeyer et al., 2019[31]	88
Niemeyer et al., 2020[30]	85
Saris et al., 2014[11]	78
Wondrasch et al., 2009[13]	82
Wondrasch et al., 2015[12]	81
Zeifang et al., 2010[32]	75

In the basic science literature, cyclical articular joint loading has been shown to strengthen cartilage at the tissue and cellular level by increasing the amount of proteoglycan in the cartilage as well as promoting neochondrogenesis to significantly improve cartilage quality and knee motion.[38,39] Furthermore, CPM may increase synovial fluid movement and joint surface articulation to help offset the complications that result from non–weight-bearing as well as affecting the nutritional transport system of the knee.[40,41] Despite the benefits illustrated by animal models, clinical evidence is lacking in quality and homogeneity to support implementation of CPM following cartilage restoration procedures. One systematic review assessed the use of CPM following cartilage repair procedures and found that the majority of studies did not describe common variables such as the duration of CPM therapy, the initiation timing of CPM therapy, and the initial ROM used.[42] The review found only 4 studies that directly examined the effect of CPM on postoperative results. In an animal model, one study[43] compared the effects of CPM and immobilization on synovitis and cartilage degeneration. The study found that in the CPM group, there was greater synovitis at 2 weeks, but at 6 weeks articular cartilage was preserved in the knees treated with CPM compared to immobilization.

In comparison, a previous systematic review[44] evaluated the rehabilitation protocols, RTP guidelines, and subsequent rates of RTP following MFx, OAT, OCA, and ACI. The study found that the majority of patients were

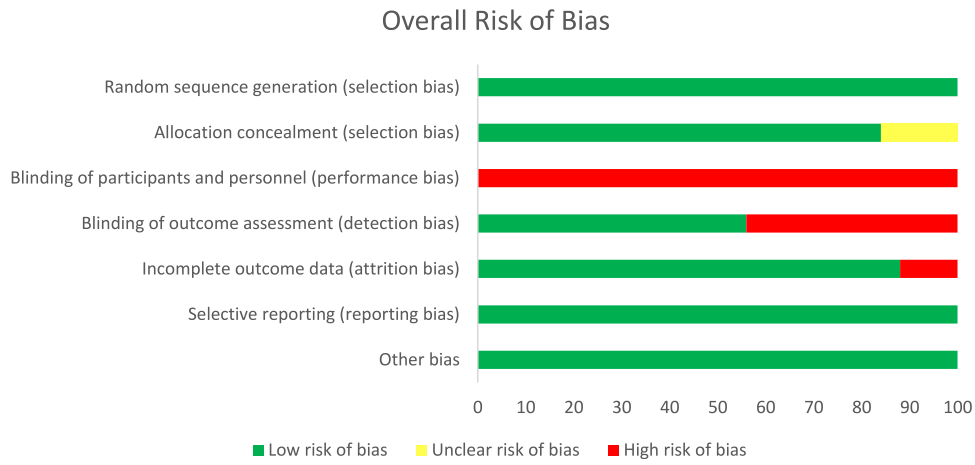

Fig 2. Risk of bias graph. Risk of bias is presented as a percentage across all included studies (green, low risk; yellow, unclear; red, high risk).

able to RTP following cartilage restoration procedures in the knee, regardless of surgical procedure used. However, while the rate of RTP at the same level was similar to the overall rate of return following OAT, there was a large number of patients unable to return to the same level following MFx, OCA, and ACI. In addition, there was wide variety in the rehabilitation protocols, and scant literature on RTP protocols.

Limitations

The limitations of this study should be noted. There was heterogeneity in the third-generation ACI products used, the various aspects of postoperative rehabilitation across studies, patient groups, and lesion size. Furthermore, this study used stringent inclusion criteria, which limits generalizability. Also, the majority of the studies came from the same author groups, with several studies published by the same research team, which may have skewed the results. Lastly, the rehabilitation protocols found in scientific studies designed to control various characteristics might not be reflective of what occurs in a clinical setting outside of a research protocol.

Conclusions

Based on the included studies, most rehabilitation protocols for third-generation ACI initiate CPM within 24 hours postoperatively and allow partial WB immediately following surgery with progression to full WB within 12 weeks. There is variation of the PT modalities used as well as the timing of their initiation.

References

1. Chubinskaya S, Haudenschild D, Gasser S, Stannard J, Krettek C, Borrelli J Jr. Articular cartilage injury and potential remedies. *J Orthop Trauma* 2015;29:S47-52 (suppl 12).
2. Dekker TJ, Aman ZS, DePhillipo NN, Dickens JF, Anz AW, LaPrade RF. Chondral lesions of the knee: An evidence-based approach. *J Bone Joint Surg Am* 2021;103:629-645.
3. Schrock JB, Kraeutler MJ, Houck DA, McQueen MB, McCarty EC. A cost-effectiveness analysis of surgical treatment modalities for chondral lesions of the knee: Microfracture, osteochondral autograft transplantation, and autologous chondrocyte implantation. *Orthop J Sports Med* 2017;5:2325967117704634.
4. Schuette HB, Kraeutler MJ, McCarty EC. Matrix-assisted autologous chondrocyte transplantation in the knee: A systematic review of mid- to long-term clinical outcomes. *Orthop J Sports Med* 2017;5:2325967117709250.
5. Kraeutler MJ, Belk JW, Carver TJ, McCarty EC. Is delayed weightbearing after matrix-associated autologous chondrocyte implantation in the knee associated with better outcomes? A systematic review of randomized controlled trials. *Orthop J Sports Med* 2018;6:2325967118770986.
6. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:5928.
7. Coleman BD, Khan HM, Maffulli N, Cook JL, Wark JD. Studies of surgical outcome after patellar tendinopathy: clinical significance of methodological deficiencies and guidelines for future studies. Victorian Institute of Sport Tendon Study Group. *Scand J Med Sci Sports* 2000;10:2-11.
8. Brittberg M, Recker D, Ilgenfritz J, Saris DBF. SUMMIT Extension Study Group. Matrix-applied characterized autologous cultured chondrocytes versus microfracture: Five-year follow-up of a prospective randomized trial. *Am J Sports Med* 2018;46:1343-1351.
9. Ebert JR, Edwards PK, Fallon M, Ackland TR, Janes GC, Wood DJ. Two-year outcomes of a randomized trial investigating a 6-week return to full weightbearing after matrix-induced autologous chondrocyte implantation. *Am J Sports Med* 2017;45:838-848.
10. Ebert JR, Fallon M, Wood DJ, Janes GC. An accelerated 6-week return to full weight bearing after matrix-induced autologous chondrocyte implantation results in good clinical outcomes to 5 years post-surgery. *Knee Surg Sports Traumatol Arthrosc* 2021;29:3825-3833.

11. Saris D, Price A, Widuchowski W, et al. Matrix-applied characterized autologous cultured chondrocytes versus microfracture: Two-year follow-up of a prospective randomized trial. *Am J Sports Med* 2014;42:1384-1394.
12. Wondrasch B, Risberg MA, Zak L, Marlovits S, Aldrian S. Effect of accelerated weightbearing after matrix-associated autologous chondrocyte implantation on the femoral condyle: a prospective, randomized controlled study presenting MRI-based and clinical outcomes after 5 years. *Am J Sports Med* 2015;43:146-153.
13. 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;37:88S-96S (suppl 1).
14. Akgun I, Unlu MC, Erdal OA, et al. Matrix-induced autologous mesenchymal stem cell implantation versus matrix-induced autologous chondrocyte implantation in the treatment of chondral defects of the knee: A 2-year randomized study. *Arch Orthop Trauma Surg* 2015;135:251-263.
15. Barié A, Kruck P, Sorbi R, et al. Prospective long-term follow-up of autologous chondrocyte implantation with periosteum versus matrix-associated autologous chondrocyte implantation: A randomized clinical trial. *Am J Sports Med* 2020;48:2230-2241.
16. Basad E, Ishaque B, Bachmann G, Stürz 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;18:519-527.
17. Clavé A, Potel JF, Servien E, et al. Third-generation autologous chondrocyte implantation versus mosaicplasty for knee cartilage injury: 2-year randomized trial. *J Orthop Res* 2016;34:658-665.
18. Crawford DC, DeBerardino TM, Williams RJ 3rd. NeoCart, an autologous cartilage tissue implant, compared with microfracture for treatment of distal femoral cartilage lesions: An FDA phase-II prospective, randomized clinical trial after two years. *J Bone Joint Surg Am* 2012;94:979-989.
19. Ebert JR, Fallon M, Ackland TR, Janes GC, Wood DJ. Minimum 10-year clinical and radiological outcomes of a randomized controlled trial evaluating 2 different approaches to full weightbearing after matrix-induced autologous chondrocyte implantation. *Am J Sports Med* 2020;48:133-142.
20. Ebert JR, Fallon M, Robertson WB, et al. Radiological assessment of accelerated versus traditional approaches to postoperative rehabilitation following matrix-induced autologous chondrocyte implantation. *Cartilage* 2011;2:60-72.
21. 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;40:1527-1537.
22. Ebert JR, Lloyd DG, Ackland T, Wood DJ. Knee biomechanics during walking gait following matrix-induced autologous chondrocyte implantation. *Clin Biomech (Bristol, Avon)* 2010;25:1011-1017.
23. 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;1:180-187.
24. Ebert JR, Robertson WB, Lloyd DG, Zheng MH, Wood DJ, Ackland T. Traditional vs accelerated approaches to postoperative rehabilitation following matrix-induced autologous chondrocyte implantation (MACI): Comparison of clinical, biomechanical and radiographic outcomes. *Osteoarthritis Cartilage* 2008;16:1131-1140.
25. Edwards PK, Ackland TR, Ebert JR. Accelerated weightbearing rehabilitation after matrix-induced autologous chondrocyte implantation in the tibiofemoral joint: Early clinical and radiological outcomes. *Am J Sports Med* 2013;41:2314-2324.
26. Fossum V, Hansen AK, Wilsgaard T, Knutsen G. Collagen-covered autologous chondrocyte implantation versus autologous matrix-induced chondrogenesis: A randomized trial comparing 2 methods for repair of cartilage defects of the knee. *Orthop J Sports Med* 2019;7:2325967119868212.
27. Hoburg A, Niemeyer P, Laute V, et al. Matrix-associated autologous chondrocyte implantation with spheroid technology is superior to arthroscopic microfracture at 36 months regarding activities of daily living and sporting activities after treatment. *Cartilage* 2021;13(1_suppl):437S-448S.
28. Ibarra C, Villalobos E, Madrazo-Ibarra A, et al. Arthroscopic matrix-assisted autologous chondrocyte transplantation versus microfracture: A 6-year follow-up of a prospective randomized trial. *Am J Sports Med* 2021;49:2165-2176.
29. Liu YL, Yen CC, Liu TT, et al. Safety and efficacy of Kartigen® in treating cartilage defects: A randomized, controlled, phase I trial. *Polymers (Basel)* 2021;13:3029.
30. Niemeyer P, Laute V, Zinser W, et al. Safety and efficacy of matrix-associated autologous chondrocyte implantation with spheroid technology is independent of spheroid dose after 4 years. *Knee Surg Sports Traumatol Arthrosc* 2020;28:1130-1143.
31. Niemeyer P, Laute V, Zinser W, et al. A prospective, randomized, open-label, multicenter, Phase III noninferiority trial to compare the clinical efficacy of matrix-associated autologous chondrocyte implantation with spheroid technology versus arthroscopic microfracture for cartilage defects of the knee. *Orthop J Sports Med* 2019;7:2325967119854442.
32. Zeifang F, Oberle D, Nierhoff C, et al. Autologous chondrocyte implantation using the original periosteum-cover technique versus matrix-associated autologous chondrocyte implantation: A randomized clinical trial. *Am J Sports Med* 2010;38:924-933.
33. Rehabilitation MACI. https://www.maci.com/healthcare-professionals/about-the-procedure/rehab.html. Accessed March 28, 2022.
34. Edwards PK, Ackland T, Ebert JR. Clinical rehabilitation guidelines for matrix-induced autologous chondrocyte

implantation on the tibiofemoral joint. *J Orthop Sports Phys Ther* 2014;44:102-119.
35. Dhillon J, Decilveo AP, Kraeutler MJ, Belk JW, McCulloch PC, Scillia AJ. Third-generation autologous chondrocyte implantation (cells cultured within collagen membrane) versus microfracture for focal chondral defects of the knee joint: A systematic review of randomized controlled trials at minimum two-year follow-up. *Arthroscopy* 2022;38:2579-2586.
36. Kraeutler MJ, Belk JW, Purcell JM, McCarty EC. Microfracture versus autologous chondrocyte implantation for articular cartilage lesions in the knee: A systematic review of 5-year outcomes. *Am J Sports Med* 2018;46:995-999.
37. Schuette HB, Kraeutler MJ, Schrock JB, McCarty EC. Primary autologous chondrocyte implantation of the knee versus autologous chondrocyte implantation after failed marrow stimulation: A systematic review. *Am J Sports Med* 2021;49:2536-2541.
38. Knapik DM, Harris JD, Pangrazzi G, et al. The basic science of continuous passive motion in promoting knee health: A systematic review of studies in a rabbit model. *Arthroscopy* 2013;29:1722-1731.
39. Saadat E, Lan H, Majumdar S, Rempel DM, King KB. Long-term cyclical in vivo loading increases cartilage proteoglycan content in a spatially specific manner: An infrared microspectroscopic imaging and polarized light microscopy study. *Arthritis Res Ther* 2006;8(R147).
40. Danzig LA, Hargens AR, Gershuni DH, Skyhar MJ, Sfakianos PN, Akeson WH. Increased transsynovial transport with continuous passive motion. *J Orthop Res* 1987;5:409-413.
41. Howard JS, Mattacola CG, Romine SE, Lattermann C. Continuous passive motion, early weight bearing, and active motion following knee articular cartilage repair: Evidence for clinical practice. *Cartilage* 2010;1:276-286.
42. Karnes JM, Harris JD, Griesser MJ, Flanigan DC. Continuous passive motion following cartilage surgery: Does a common protocol exist? *Phys Sportsmed* 2013;41:53-63.
43. Kim HK, Kerr RG, Cruz TF, Salter RB. Effects of continuous passive motion and immobilization on synovitis and cartilage degradation in antigen induced arthritis. *J Rheumatol* 1995;22:1714-1721.
44. Hurley ET, Davey MS, Jamal MS, et al. Return-to-play and rehabilitation protocols following cartilage restoration procedures of the knee: A systematic review. *Cartilage* 2021;13(1_suppl):907S-914S.